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ALDURAZYME® (LARONIDASE)

Solution for Intravenous Infusion Only

DESCRIPTION

ALDURAZYME® (laronidase) is a polymorphic variant of the human enzyme, α-L-iduronidase that is produced by recombinant DNA technology in a Chinese hamster ovary cell line. α-L-iduronidase (glycosaminoglycan α-L-iduronohydrolase, EC 3.2.1.76) is a lysosomal hydrolase that catalyses the hydrolysis of terminal α-L-iduronic acid residues of dermatan sulfate and heparan sulfate.

Laronidase is a glycoprotein with a molecular weight of approximately 83 kD. The predicted amino acid sequence of the recombinant form, as well as the nucleotide sequence that encodes it, are identical to a polymorphic form of human α-L-iduronidase. The recombinant protein is comprised of 628 amino acids after cleavage of the N-terminus and contains 6 N-linked oligosaccharide modification sites. Two oligosaccharide chains terminate in mannose-6-phosphate sugars. ALDURAZYME has a specific activity of approximately 172 U/mg.

ALDURAZYME, for intravenous infusion, is supplied as a sterile, nonpyrogenic, colorless to pale yellow, clear to slightly opalescent solution that must be diluted prior to administration in 0.9% Sodium Chloride Injection, USP, containing 0.1% Albumin (Human). The solution in each vial contains a nominal laronidase concentration of 0.58 mg/mL and a pH of approximately 5.5. The extractable volume of 5.0 mL from each vial provides 2.9 mg laronidase, 43.9 mg sodium chloride, 63.5 mg sodium phosphate monobasic monohydrate, 10.7 mg sodium phosphate dibasic heptahydrate, and 0.05 mg polysorbate 80. ALDURAZYME does not contain preservatives; vials are for single use only.

CLINICAL PHARMACOLOGY

Mechanism of Action

Mucopolysaccharide storage disorders are caused by the deficiency of specific lysosomal enzymes required for the catabolism of glycosaminoglycans (GAG). Mucopolysaccharidosis I (MPS I) is characterized by the deficiency of α-L-iduronidase, a lysosomal hydrolase which catalyses the hydrolysis of terminal α-L-iduronic acid residues

of dermatan sulfate and heparan sulfate. Reduced or absent α-L-iduronidase activity results in the accumulation of the GAG substrates, dermatan sulfate and heparan sulfate, throughout the body and leads to widespread cellular, tissue, and organ dysfunction.

The rationale of ALDURAZYME therapy in MPS I is to provide exogenous enzyme for uptake into lysosomes and increase the catabolism of GAG. ALDURAZYME uptake by cells into lysosomes is most likely mediated by the mannose-6-phosphate-terminated oligosaccharide chains of laronidase binding to specific mannose-6-phosphate receptors.

Because many proteins in the blood are restricted from entry into the central nervous system by the blood brain barrier, effects of intravenously administered ALDURAZYME on cells within the central nervous system (CNS) cannot be inferred from activity in sites outside the CNS. The ability of ALDURAZYME to cross the blood brain barrier has not been evaluated in animal models or in clinical trials.

Pharmacokinetics

The pharmacokinetics of laronidase were evaluated in 12 patients with MPS I who received 0.58 mg/kg of ALDURAZYME as a 4 hour infusion. After the 1st, 12th and 26th weekly infusions, the mean maximum plasma concentrations (C_{max}) ranged from 1.2 to 1.7 mcg/mL for the 3 time points. The mean area under the plasma concentration-time curve (AUC_{∞}) ranged from 4.5 to 6.9 mcg• hour/mL. The mean volume of distribution (V_z) ranged from 0.24 to 0.6 L/kg. Mean plasma clearance (CL) ranged from 1.7 to 2.7 mL/min/kg, and the mean elimination half-life ($t_{1/2}$) ranged from 1.5 to 3.6 hours.

Effects of Antibodies

Most patients who received once-weekly infusions of ALDURAZYME developed antibodies to laronidase by week 12. Between weeks 1 and 12, increases in plasma clearance of laronidase were observed in some patients which appeared to be proportional to the antibody titer. At week 26, plasma clearance of laronidase was comparable to that at week 1, in spite of the continued and, in some cases, increased titers of antibodies.

CLINICAL STUDIES

ALDURAZYME was studied in a randomized, placebo-controlled clinical trial of 45 MPS I patients of whom 1 patient was clinically assessed as having the Hurler form, 37 Hurler-Scheie, and 7 Scheie. All patients had a baseline forced vital capacity (FVC) less than or

equal to 77% of predicted. Patients received ALDURAZYME at 0.58 mg/kg or placebo once-weekly for 26 weeks. All patients were treated with antipyretics and antihistamines prior to each infusion.

The primary efficacy outcome assessments were FVC and distance walked in 6 minutes (6-minute walk test, 6MWT). After 26 weeks, patients treated with ALDURAZYME showed improvement in FVC and in 6MWT compared to placebo-treated patients (see **Table 1**).

Table 1: Primary Efficacy Outcomes

		ALDURAZYME N = 22	Placebo N = 23
Forced Vital Capacity (percent of predicted normal)			
Baseline	Mean ± s.d.	48 ±15	54 ±16
Week 26	Mean ± s.d.	50 ±17	51 ±13
Change from baseline to week 26	Mean ± s.d.	1±7	-3±7
	Median	1	-1
Difference between groups	Mean	4	
	Median (95% CI)	2 (0.4, 7)	p=0.02*
6-Minute Walk Distance (meters)			
Baseline	Mean ± s.d.	319 ± 131	367 ±114
Week 26	Mean ± s.d.	339± 127	348 ±129
Change from baseline to week 26	Mean ± s.d.	20 ± 69	-18 ± 67
	Median	28	-11
Difference between groups	Mean	38	
	Median (95% CI)	39 (-2, 79)	p=0.07*

* By Wilcoxon Rank Sum Test

Evaluations of bioactivity were changes in liver size and urinary GAG levels. Liver size and urinary GAG levels decreased in patients treated with ALDURAZYME compared to patients treated with placebo. No subject in the group receiving ALDURAZYME reached the normal range for urinary GAG levels during this 6-month study.

All 45 patients received open-label ALDURAZYME for 36 weeks following the double-blind period. Maintenance of mean FVC and an additional increase in mean 6MWT distance were observed compared to the start of the open-label period among patients who were initially randomized to and then continued to receive ALDURAZYME. Among patients who had been initially randomized to placebo, improvements from baseline in mean FVC and 6MWT distance were observed compared to the start of the open-label period.

INDICATIONS AND USAGE

ALDURAZYME is indicated for patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I) and for patients with the Scheie form who have moderate to severe symptoms. The risks and benefits of treating mildly affected patients with the Scheie form have not been established.

ALDURAZYME has been shown to improve pulmonary function and walking capacity. ALDURAZYME has not been evaluated for effects on the central nervous system manifestations of the disorder.

CONTRAINDICATIONS

There are no known contraindications to the use of ALDURAZYME.

WARNINGS

Hypersensitivity Reactions

Patients treated with ALDURAZYME may develop infusion-related hypersensitivity reactions (see **ADVERSE REACTIONS**). In the clinical studies, one patient developed an anaphylactic reaction approximately three hours after the initiation of the infusion. The reaction consisted of urticaria and airway obstruction. Resuscitation required an emergency tracheostomy. This patient's pre-existing MPS I related upper airway obstruction may have contributed to the severity of this reaction (see **ADVERSE REACTIONS: Infusion-Related Reactions** and **Immunogenicity**).

Some infusion-related reactions may be ameliorated by slowing the rate of infusion or treatment with additional antipyretics and/or antihistamines. If severe hypersensitivity or anaphylactic reactions occur, immediately discontinue the infusion of ALDURAZYME and initiate appropriate treatment. Caution should be exercised if epinephrine is being considered for use in patients with MPS I due to the increased prevalence of coronary artery disease in these patients.

The risks and benefits of re-administering ALDURAZYME following a severe hypersensitivity or anaphylactic reaction should be considered. Extreme care should be exercised, with appropriate resuscitation measures available, if the decision is made to re-administer the product.

PRECAUTIONS

General

Patients should receive antipyretics and/or antihistamines prior to infusion (see **WARNINGS** and **ADVERSE REACTIONS**). If an infusion reaction occurs, regardless of pre-treatment, decreasing the infusion rate, temporarily stopping the infusion, and/or administration of additional antipyretics and/or antihistamines may ameliorate the symptoms.

Information for Patients

Patients should be informed that a registry for MPS I patients has been established in order to better understand the variability and progression of MPS I disease, and to continue to monitor and evaluate treatments. Patients should be encouraged to participate and advised that their participation may involve long-term follow-up. Information regarding the registry program may be found at www.MPSIregistry.com or by calling (800) 745-4447.

Drug Interactions

No formal drug interaction studies have been conducted.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to assess the mutagenic and carcinogenic potential of ALDURAZYME have not been conducted.

Reproductive studies in rats have not demonstrated impairment of fertility (see **PRECAUTIONS: Pregnancy**).

Pregnancy: Category B

Reproduction studies have been performed in male and female rats at doses up to 6.2 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ALDURAZYME. However, there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ALDURAZYME should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ALDURAZYME is administered to a nursing woman (see **PRECAUTIONS: Information for Patients** regarding a registry program. Nursing women are encouraged to participate in this program.).

Pediatric Use

Patients younger than 5 were not included in the clinical studies because of inability to comply with efficacy outcome assessments. It is not known if children younger than 5 respond differently from older children.

Geriatric Use

Clinical studies of ALDURAZYME did not include patients aged 65 and over. It is not known whether they respond differently from younger patients.

ADVERSE REACTIONS

The most serious adverse reaction reported with ALDURAZYME was an anaphylactic reaction consisting of urticaria and airway obstruction, which occurred in one patient. Pre-existing upper airway obstruction may have contributed to the severity of the reaction (see **WARNINGS: Hypersensitivity Reactions**).

The most common adverse reactions associated with ALDURAZYME treatment in the clinical studies were upper respiratory tract infection, rash, and injection site reaction.

The most common adverse reactions requiring intervention were infusion-related reactions, particularly flushing. Most infusion-related reactions requiring intervention were ameliorated with slowing of the infusion rate, temporarily stopping the infusion, and/or administering additional antipyretics and/or antihistamines.

The data described below reflect exposure to 0.58 mg/kg of ALDURAZYME for 26 weeks in a placebo-controlled double-blind study in 45 patients with MPS I (N=22 ALDURAZYME, and N=23 placebo). All 45 patients continued into an open-label study of ALDURAZYME treatment for an additional 36 weeks. An additional 10 patients participated in a Phase 1 open-label study with continued infusions for up to 3 years. The population in the placebo-controlled study was evenly distributed for gender (N=23 females and 22 males) and ranged in ages from 6 to 43 years. Of the 45 patients in the placebo-controlled study, 1 was clinically assessed as having Hurler form, 37 Hurler-Scheie, and 7 Scheie. All patients were treated with antipyretics and antihistamines prior to the infusions.

Because clinical trials are conducted under widely varying and controlled conditions, the observed adverse reaction rates may not predict the rates observed in patients in clinical practice.

Table 2 enumerates adverse events and selected laboratory abnormalities that occurred during the placebo-controlled trial in at least 2 patients more in the ALDURAZYME group than was observed in the placebo group. Reported adverse events have been classified using standard WHOART terms. Observed adverse events in the Phase 1 study and the open-label treatment period following the controlled study were not different in nature or severity.

Table 2: Number and (%) of Patients with Adverse Events and Selected Laboratory Abnormalities in the Placebo-Controlled Study

Adverse Event	Placebo (N = 23)	ALDURAZYME (N = 22)
Respiratory System		
Upper respiratory tract infection	4 (17)	7 (32)
Body as a Whole		
Chest pain	0	2 (9)
Nervous System		
Hyperreflexia	0	3 (14)
Paresthesia	1 (4)	3 (14)
Skin and Appendages		
Rash	5 (22)	8 (36)
Resistance Mechanism		
Abscess	0	2 (9)
Liver and Biliary System		
Bilirubinemia	0	2 (9)
Vascular		
Vein disorder	1 (4)	3 (14)
Urinary System		
Facial edema	0	2 (9)
Cardiovascular, General		
Hypotension	0	2 (9)
Dependent edema	0	2 (9)
Vision		
Corneal opacity	0	2 (9)
Application Site		
Injection site pain	0	2 (9)
Injection site reaction	2 (9)	4 (18)
Platelet, Bleeding and Clotting		
Thrombocytopenia	0	2 (9)

Infusion-Related Reactions

Infusion-related reactions were reported in 7 of 22 patients treated with ALDURAZYME. Infusion-related reactions were not significantly different between the ALDURAZYME treatment group and the placebo group who received infusions of diluent and all components of ALDURAZYME except the laronidase enzyme. The most common infusion-related reactions included flushing, fever, headache and rash. Flushing occurred in 5 patients (23%) receiving ALDURAZYME; the other reactions were less frequent. All reactions were mild to moderate in severity. The frequency of infusion-related reactions decreased with continued use during the open-label extended use period. There was one case of anaphylaxis during the open-label extension period (see **WARNINGS** and **ADVERSE REACTIONS: Immunogenicity**). Less common infusion-related reactions include cough, bronchospasm, dyspnea, urticaria, angioedema and pruritus.

Immunogenicity

Fifty of 55 patients (91%) treated with ALDURAZYME were positive for antibodies to laronidase. The clinical significance of antibodies to ALDURAZYME is not known, including the potential for product neutralization.

The data reflect the percentage of patients whose test results were considered positive for antibodies to ALDURAZYME using an enzyme-linked immunosorbent assay (ELISA) for laronidase-specific IgG binding antibodies, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibodies in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ALDURAZYME with the incidence of antibodies to other products may be misleading.

Four patients in the controlled study who experienced severe infusion-related reactions were tested for ALDURAZYME specific IgE antibodies and complement activation. IgE testing was performed by ELISA and complement activation was measured by the Quidel Enzyme Immunoassay. One of the four patients had an anaphylactic reaction consisting of urticaria and airway obstruction and tested positive for both ALDURAZYME specific IgE binding antibodies and complement activation (see **WARNINGS: Hypersensitivity Reactions**).

Other hypersensitivity reactions were also seen in patients receiving ALDURAZYME (see **ADVERSE REACTIONS: Infusion-Related Reactions**).

OVERDOSAGE

There is no experience with overdoses of ALDURAZYME.

DOSAGE AND ADMINISTRATION

The recommended dosage regimen of ALDURAZYME is 0.58 mg/kg of body weight administered once-weekly as an intravenous infusion.

Pretreatment with antipyretics and/or antihistamines is recommended 60 minutes prior to the start of the infusion (see **PRECAUTIONS: General**).

The total volume of the infusion is determined by the patient's body weight and should be delivered over approximately 3 to 4 hours. Patients with a body weight of 20 kg or less should receive a total volume of 100 mL. Patients with a body weight of greater than 20 kg should receive a total volume of 250 mL. The initial infusion rate of 10 mcg/kg/hr may be incrementally increased every 15 minutes during the first hour, as tolerated, until a maximum infusion rate of 200 mcg/kg/hr is reached. The maximum rate is then maintained for the remainder of the infusion (2-3 hours).

For Patients Weighing 20 kg or Less

Total Volume of ALDURAZYME Infusion = 100 mL	
2 mL/hr x 15 minutes (10 mcg/kg/hr)	Obtain vital signs, if stable then increase the rate to...
4 mL/hr x 15 minutes (20 mcg/kg/hr)	Obtain vital signs, if stable then increase the rate to...
8 mL/hr x 15 minutes (50 mcg/kg/hr)	Obtain vital signs, if stable then increase the rate to...
16 mL/hr x 15 minutes (100 mcg/kg/hr)	Obtain vital signs, if stable then increase the rate to...
32 mL/hr x ~3 hours (200 mcg/kg/hr)	For the remainder of the infusion.

For Patients Weighing Greater than 20 kg

Total Volume of ALDURAZYME Infusion = 250 mL	
5 mL/hr x 15 minutes (10 mcg/kg/hr)	Obtain vital signs, if stable then increase the rate to...
10 mL/hr x 15 minutes (20 mcg/kg/hr)	Obtain vital signs, if stable then increase the rate to...
20 mL/hr x 15 minutes (50 mcg/kg/hr)	Obtain vital signs, if stable then increase the rate to...
40 mL/hr x 15 minutes (100 mcg/kg/hr)	Obtain vital signs, if stable then increase the rate to...
80 mL/hr x ~3 hours (200 mcg/kg/hr)	For the remainder of the infusion.

Each vial of ALDURAZYME provides 2.9 mg of laronidase in 5.0 mL of solution and is intended for single use only. Do not use the vial more than one time. The concentrated solution for infusion must be diluted with 0.1% Albumin (Human) in 0.9% Sodium Chloride Injection, USP using aseptic techniques. ALDURAZYME should be prepared using PVC Containers and administered with a PVC infusion set equipped with an in-line, low protein binding 0.2 micrometer (μm) filter. There is no information on the compatibility of diluted ALDURAZYME with glass containers.

Instructions for Use (Aseptic Techniques)

1. Determine the number of vials to be diluted based on the individual patient's weight and the recommended dose of 0.58 mg/kg [Patient's weight (kg) x 1 mL/kg of ALDURAZYME = Total # mL of ALDURAZYME, then Total # of mL of ALDURAZYME ÷ 5 mL per Vial = Total # of Vials]. Round up to the nearest whole vial. Remove the required number of vials from the refrigerator to allow them to reach room temperature. Do not heat or microwave vials.
2. Before withdrawing the ALDURAZYME from the vial, visually inspect each vial for particulate matter and discoloration. The ALDURAZYME solution should be clear to slightly opalescent and colorless to pale yellow. A few translucent particles may be present. Do not use if the solution is discolored or if there is particulate matter in the solution.
3. Determine the total volume of the infusion to be used based on the patient's body weight. The total final volume should be either 100 mL (if weight is less than or equal to 20 kg) or 250 mL (if weight is greater than 20 kg).
4. Using the chart below, prepare an infusion bag of 0.1% Albumin (Human) in 0.9% Sodium Chloride Injection, USP. Remove and discard a volume of 0.9% Sodium Chloride Injection, USP equal to the volume of Albumin (Human) to be added to the infusion bag. Add the appropriate volume of Albumin (Human) to the infusion bag and gently rotate the infusion bag to ensure proper distribution of the Albumin.

Total Volume of ALDURAZYME Infusion	Volume of Albumin (Human) 5% to be Added	Volume of Albumin (Human) 25% to be Added
100 mL	2 mL	0.4 mL
250 mL	5 mL	1 mL

5. Withdraw and discard a volume of the 0.1% Albumin (Human) in 0.9% Sodium Chloride Injection, USP from the infusion bag, equal to the volume of ALDURAZYME concentrate to be added.

6. Slowly withdraw the calculated volume of ALDURAZYME from the appropriate number of vials using caution to avoid excessive agitation. Do not use a filter needle, as this may cause agitation. Agitation may denature ALDURAZYME, rendering it biologically inactive.
7. Slowly add the ALDURAZYME solution to the 0.1% Albumin (Human) in 0.9% Sodium Chloride Injection, USP using care to avoid agitation of the solutions. Do not use a filter needle.
8. Gently rotate the infusion bag to ensure proper distribution of ALDURAZYME. Do not shake the solution.

ALDURAZYME does not contain any preservatives, therefore after dilution with saline in the infusion bags, any unused product or waste material should be discarded and disposed of in accordance with local requirements.

ALDURAZYME must not be mixed with other medicinal products in the same infusion.

The compatibility of ALDURAZYME in solution with other products has not been evaluated.

STORAGE

Store ALDURAZYME under refrigeration at 2°C to 8°C (36°F to 46°F). DO NOT FREEZE OR SHAKE. DO NOT USE ALDURAZYME after the expiration date on the vial. This product contains no preservatives.

The diluted solution should be used immediately. If immediate use is not possible, the diluted solution should be stored refrigerated at 2°C to 8°C (36°F to 46°F). The in-use storage should not be longer than 36 hours from the time of preparation to completion of administration. Room temperature storage of diluted solution is not recommended.

HOW SUPPLIED

ALDURAZYME is supplied as a sterile solution in clear Type I glass 5 mL vials (2.9 mg laronidase per 5 mL). The closure consists of a siliconized butyl stopper and an aluminum seal with a plastic flip-off cap.

NDC 58468-0070-1

Rx Only

ALDURAZYME is manufactured by:
BioMarin Pharmaceutical Inc.
371 Bel Marin Keys Blvd.
Suite 210
Novato, CA 94949
US License Number 1649

ALDURAZYME is distributed by:
Genzyme Corporation
One Kendall Square
Cambridge, MA 02139
1-800-745-4447 (phone)

STN125058/0

TOXICOLOGIST'S REVIEW

BLA: STN 125058
SPONSOR: Biomarin Pharmaceutical Inc.
PRODUCT: recombinant human a-iduronidase; rhIDU; laronidase; Aldurazyme™
FORMULATION/CHEMISTRY: Isolated from cell culture supernatant after growth of CHO cells transfected with a recombinant expression vector encoded for rhIDU. Formulated as a sterile, liquid solution of polysorbate 80 (10 µg/ml, 0.05 mg) in a sodium chloride (150 mM, 43.9 mg) and sodium phosphate buffer (92 mM, 63.5 mg). The drug product is to be diluted for intravenous administration with between 100ml to 250ml of 0.9% sodium chloride solution. The final product (2.90 mg/ vial, 100 units/ml), is reconstituted with 5 mL of Water for Injection USP.
PROPOSED INDICATION: Long term enzyme replacement therapy in patients with Mucopolysaccharidosis I (MPS I; a-l-iduronidase deficiency) to treat the non-central nervous system manifestations of the disease
ABBREVIATIONS: recombinant human a-iduronidase = rhIDU, intravenous = IV, glycosaminoglycan = GAG; MPS I = Mucopolysaccharidosis I, (α-L-iduronidase deficiency)

Application History

BL125058/0.00: Original submission of rolling BLA 26-JUL-2002
BL125058/0.01: Preclinical Toxicology Update 04-SEP-2002
BL125058/0.02: Neutralizing Antibody Data for Phase 3 (ALID-003-99) 10-OCT -2002
BL125058/0.03: Additional Dataset % Predicted Normal FVC Phase 3 (ALID-003-99) 17-OCT -2002
BL125058/0.04: 36-Week Efficacy Data for Phase 3 Ext. (ALID-006-01) 24-OCT-2002
BL125058/0.05: 120-Day Update 05-DEC-2002
BL125058/0.06: Responses to the Discipline Review Letter for the CMC 09-DEC -2002
BL125058/0.07: 120-Day Update: CRTs & Programs 12-DEC-2002
BL125058/0.08: Clarification: Number of Bioreactors for Cell Culture of Laronidase 19-DEC –2002

CROSS-REFERENCES: BB-IND ----------

Table of Contents

Introduction

The target agent, Aldurazyme™ (laronidase) is a recombinant form of human a-iduronidase enzyme, which is a monomeric protein with a molecular weight of 83kD by ---------- analysis. Laronidase is a 628 amino acid lysosomal hydrolase that cleaves iduronic acid residues from the non-reducing ends of heparan sulfate and dermatan sulfate. The enzyme is a single polypeptide chain of molecular mass ---------- ---------- and a molecular formula of ---------- contains six asparagine-linked glycosylation sites, two of which carry the bis mannose-6-phosphate oligomannose7 oligosaccharide that binds the target cell surface receptor. The apparent increase in molecular mass of -- kD over that predicted by the amino acid sequence is a result of posttranslational modifications.

Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder located at 4p16.3. In the human, α-L-iduronidase deficiency results in a spectrum of clinical manifestations and disease severities. These manifestations are directly related to accumulation of glycosaminoglycans (GAGs), primarily dermatan and heparan sulfate, as a result of the lysosomal enzyme deficiency. The clinical spectrum is conventionally categorized into three overlapping clinical syndromes that vary in clinical severity. These are in order of decreasing clinical severity, Hurler syndrome (MPS1H), Hurler-Scheie Syndrome (MPS IH-S), and Scheie Syndrome (MPS-IS). The three syndromes are indistinguishable on the basis of the routine clinical chemistry measures as all three exhibit only minimal enzyme activity and all show elevated urinary GAG levels the ranges of which overlap. Further although the classical diagnostic criteria are clinical,

they also overlap and the designation of an individual into a particular diagnostic category is somewhat subjective. In general Hurler patients present within the first year multiple of the following findings: coarse facies, skeletal deformities, prominent forehead, hernia (umbilical or inguinal), enlarged tongue, short stature, joint stiffness, acute cardiomyopathy associated with endocardial fibroelastosis, developmental delay that progressively increases, deafness, recurring upper respiratory tract and ear infections, obstructive airway disease, sleep apnea, noisy breathing, persistent copious nasal discharge, corneal clouding, and occasionally communicating hydrocephalus associated with increased intracranial pressure. Death usually occurs within the first decade of life. Patients classified as Hurler-Sheie patients typically present later (between the ages of 3 and 8) with milder symptoms. These symptoms include hepatosplenomegaly, obstructive airway disease and sleep apnea, recurring respiratory infections, dysostosis multiplex, short stature, characteristic coarse facies, corneal clouding, joint stiffness, deafness, and valvular heart disease. The life expectancy for these patients is to reach young adulthood. Unlike Hurler patients, Hurler-Scheie patients achieve normal developmental milestones. The patients with the mildest MPS I deficiency phenotype, Sheie Syndrome are usually diagnosed in the teen years and the presenting symptoms are often joint stiffness, aortic valve disease, mild hepatosplenomegaly or corneal clouding. These patients have little or no neurological manifestations, a normal stature and may live a normal lifespan with only minimal clinical symptoms and few restrictions on activities of daily living.

The proposed clinical indication for Aldurazyme™ (laronidase) is "long term enzyme replacement therapy in patients with Mucopolysaccharidosis I (MPS I; α-L-iduronidase deficiency) to treat the non-central nervous system manifestations of the disease". In the submitted package insert the sponsor recommended the following dosage regimen-

"The recommended dosage regimen of Aldurazyme™ is 100 U/kg (0.58 mg/kg) of actual body weight administered once weekly as an intravenous infusion."

With initial administrations of Aldurazyme™, it is recommended that patients be administered pretreatment medications approximately 60 minutes prior to the start of the infusion. If clinically indicated, the administration of pretreatment medications should continue with subsequent infusions of Aldurazyme™.

The total volume of the infusion is determined by the patient's actual body weight and should be delivered over approximately 3 to 4 hours. Patients with an actual body weight of 20 kg or less should receive a total volume of 100 mL. Patients with an actual body weight of greater than 20 kg should receive a total volume of 250 mL. The initial infusion rate of 2 U/kg/hr may be incrementally increased every 15 minutes during the first hour, as tolerated, until a maximum infusion rate of 43 U/kg/hr is reached. The maximum rate is then maintained for the remainder of the infusion (2-3 hours).

Each vial of Aldurazyme™ contains 500 U (100 U/mL; 0.58 mg/mL) of laronidase and is intended for single use only. The concentrate for solution for infusion must be diluted with 0.1% Human Serum Albumin in 0.9% Sodium Chloride for Injection, USP using aseptic techniques. In the absence of stability studies using glass containers, it is recommended that Aldurazyme™ be prepared and administered using PVC Containers. It is recommended that the Aldurazyme™ solution be administered with a PVC infusion set equipped with an in-line, low protein binding 0.2 micrometer (μm) filter.

The primary trial used to demonstrate Aldurazyme™ was a single randomized, placebo-controlled clinical trial of 45 MPS I patients, of whom 1 was classified as having the Hurler form, 37 Hurler-Scheie, and 7 Scheie. All patients had a baseline forced vital capacity (FVC) less than or equal to 80% of predicted. Patients received Aldurazyme™ at 0.58mg/kg or placebo once weekly for 26 weeks. In clinical studies the most significant adverse reactions were infusion related-reactions of varying clinical intensities as were seen in the preclinical studies. As a result in the Phase 3 Studies, all patients were pretreated prior to each infusion with age-appropriate dosages of antihistamines and antipyretics, such as diphenhydramine or hydroxyzine and acetaminophen or ibuprofen, respectively.

The principal efficacy outcome assessments were FVC and distance walked in 6 minutes (6 minute walk test, 6MWT). After 26 weeks, AldurazymeTM-treated patients showed improvement in FVC and in the 6MWT compared to placebo-treated patients. Evaluations of bioactivity were changes in liver size and urinary GAG levels. Liver size and urinary GAG levels were decreased in Aldurazyme™ treated patients compared to placebo-treated patients. No subject in the Aldurazyme™-treated group reached the normal range for urinary GAG levels during this study.

Preclinical Pharmacology Studies

Notes of clarification

Note that during preclinical development of rhIDU drug product, the assay for a-L-iduronidase activity was changed to make it more reproducible and robust and the definition of a unit was changed to be more conventional. In addition, the —

The sponsor provided an overview of the doses administered in all studies with dose conversions for all studies in the BLA submission. For clarity, doses are presented in mg/kg utilizing the new units throughout this BLA review, in order to facilitate comparison to the recommended human dose.

Also note that the dates presented with each study are the dates the report was issued, not the date of study completion when report issued date is available. This convention will be used throughout this BLA review.

Assay for rhIDU activity in animal studies

List of Pharmacology Studies

1. IDU-PC-002: Short-term Intravenous Infusion Study of Recombinant Human α-L-Iduronidase in a Single Dog, non-GLP, Conducted at----------, 11/93, Lots no. ----------

2. IDU-PC-003: Acute intravenous infusion study of recombinant human α-L-Iduronidase in a single dog; non-GLP, Conducted at----------, 4/95, Lots no. -----

3. IDU-PC-004: Subchronic Intravenous Infusion Study of Recombinant Human α-L-Iduronidase in Dogs: 4/94, non-GLP, Conducted at----------, Lots nos. -----

4. IDU-PC-005: Thirteen-Month Intravenous Infusion Study of Recombinant Human a-L-Iduronidase in a Dog: non-GLP, Conducted at----------, 1/95, Lot nos. -----

5. IDU-PC-006: 74-Week Intravenous Infusion Study of Recombinant Human a-L-Iduronidase in Dogs: 3/99, non-GLP, Conducted at----------, Lot nos. ----------

6. IDU-PC-008: Comparison of Continuous and Bolus Intravenous Infusions of Recombinant Human α-L-Iduronidase in Dogs, non-GLP, Conducted at ---------- ----------, 02/01, Lot no. ---.

7. Kakkis et al.: Enzyme replacement therapy in feline mucopolysaccharidosis I, N/A, Lot nos. -----

Review of Pharmacology Studies

1. IDU-PC-002: Short-term Intravenous Infusion Study of Recombinant Human α-L-Iduronidase in a Single Dog: Multi-step intravenous dose regimen study in a single dog. Part 1- 0.116mg/kg IV every other day for 7 doses (12 days), part 2 - IV three doses every other day for 5 days starting two months after the first dose, part 3- one IV dose (0.116 mg/kg) five months after the first dose. Levels of IDU increased in liver biopsy after treatment. Histopathology reportedly shows decreased cellular vacuolation in live and normalization of the histology of hepatocytes and Kupffer cells.

2. IDU-PC-003 One control female MPS I dog and two laronidase treated 0.58 mg/kg IV (one male and one female) MPSI dogs every other day for 5 doses (days1, 2,5,8,10) with sacrifice on day 12. Levels of IDU increased relative to untreated MPS I dogs in all tissues sampled (liver, spleen, lung, kidney, cerebrum, heart valve, myocardium, lymph node, and cornea).

3. IDU-PC-004: Subchronic Intravenous Infusion Study of Recombinant Human α-L- Iduronidase in Dogs. 2 untreated MPS I dogs and 3 MPS I dogs treated intravenously with 0.116 mg/kg rhIDU weekly for 3 months. Levels of IDU in liver greater than that in normal dog liver and spleen, other tissues less than normal dog but elevated relative to MPS I control. Histopathologic analysis showed decreased cellular vacuolation in liver, kidney and spleen.

4. IDU-PC-005: Thirteen-Month Intravenous Infusion Study of Recombinant Human α-L-Iduronidase in a Dog. Study of weekly intravenous infusion of 0.116 mg/kg for 74 weeks. Activity of a-L-Iduronidase increased in all tissues measured versus control levels in MPS I dog. Levels of IDU in liver greater than that in normal dog liver, other tissues less than normal dog but elevated relative to MPS I control. The GAG accumulation was decreased but still above normal. Histopathologic analysis showed persistent GAG accumulation in liver, kidney, adrenal gland, lung, lymph node, small intestine, spleen, synovium, gall bladder despite decreased cellular vacuolation.

5. IDU-PC-006: 74-Week Intravenous Infusion Study of Recombinant Human α-L-Iduronidase in Dogs: Uncontrolled intravenous dose-ranging study in MPSI dog model. Two dogs dosed with 0.058-0.58 mg/kg IV 1-2 times a week for weeks 1-7, then with 0.58 mg/kg IV 3 times a week for weeks 8-46, then once per week with 0.58 mg/kg IV for weeks 47-74. Results show a-L-Iduronidase activity approaching normal in liver, intestine, kidney, lung, lymph nodes, spleen, myocardium, synovium, and rib cartilage, all other tissues are less than normal. GAG accumulation decreased in all tissues relative to beginning and still above normal. Histopathology show depleted accumulation in macrophages in all tissues except CNS and dense connective tissue. Clinical improvement noted.

6. IDU-PC-008: Comparison of Continuous and Bolus Intravenous Infusions of Recombinant Human α-L-Iduronidase in Dogs: Two untreated and seven treated MPS I dogs were treated intravenously with laronidase. Two animals treated with 0.58 mg/kg and three with 2.32 mg/kg for continuous infusion for 10-39 weeks, and two dogs treated weekly for 10 weeks. Results show a-I-Iduronidase activity increased in all tissues measured relative to MPSI control animals. Levels were greater than normal canine levels in liver, spleen, kidney, lymph nodes, rib cartilage, synovium, and tracheal cartilage after both continuous and bolus infusions. GAG accumulation decreased to within or > 2-fold the normal range for kidney, liver, lung, lymph nodes, spleen, and synovium after more than one dosing interval. No reductions seen in heart valve or brain. Histopathologic information in macrophages, lymph nodes, spleen and liver reduced more by bolus than continuous infusion and with a positive dose response. No decrease in GAG vacuolation in CNS or dense connective tissue.

7. Kakkis et al., Mol. Genet. Metab. 2001. Dose ranging study in MPS I deficient cats. MPS I cats were treated intravenously for up to six months. Three were treated with 0.116 mg/kg weekly for three months, one was treated with 0.58 mg/kg IV weekly for three months in the first part of the study. In the second part of the study, one cat was treated with 0.116 mg/kg IV weekly and one cat was treated with 0.58 mg/kg IV weekly for six months. The a-L-Iduronidase activity was increased relative to controls with all tissues measured except brain, and rib cartilage, GAG accumulation was decreased to the normal range in liver, spleen and lung.

PK/ADME Studies

List of PK/ADME Studies

1. IDU-PC-001: Clearance and Tissue Distribution Study of Recombinant Human α-L-Iduronidase in Dogs: non- GLP, Conducted by ----------9/93, Lots no. ----------

2. IDU-PC-008: Comparison of Continuous and Bolus Intravenous Infusions of Recombinant Human a-L-Iduronidase in Dogs, non-GLP, Conducted at ---------- ----------, 2/01, Lot no. ----.

Review of PK/ADME Studies

1. IDU-PC-001: Clearance and Tissue Distribution Study of Recombinant Human α-L-Iduronidase in Dogs: One female MPS I dog was treated daily with 0.116 mg/kg for days 1 and 2. Result: Biphasic clearance: $t_{1/2}$ α = 0.9 minutes, $t_{1/2}$ β = 18.9 minutes.

2. IDU-PC-008: Comparison of Continuous and Bolus Intravenous Infusions of Recombinant Human a-L-Iduronidase in Dogs: Two MPS I dogs (one male, one female) were treated once during weeks 2 and 10 with 2.32 mg/kg IV. Results: Week 2- Biphasic clearance, $t_{1/2}$ α = 0.9 minutes, $t_{1/2}$ β = 59.5 and 94.9 minutes. Week 10- Monophasic clearance, $t_{1/2}$ = 66.2 and 23.8 minutes. V_c = approximately 60 ml/kg. AUC (U/ml-hr) increased from week 2 (269 and 407) to week (13364 and 2559). Clearance from (ml/kg/min) decreased from week 2 (31.0 and 20.5) to week 10 (0.62 and 3.26).

Preclinical Toxicology Studies

List of Preclinical Toxicology Studies:

1. IDU-PC-007: An acute intravenous toxicity study in rats. GLP, conducted at---------- No. 0406RB31.001, 3/01, Lot No.----------.

2. IDU-PC-009: 26-week intravenous infusion toxicity study with recombinant human a-L-Iduronidase in monkeys with a 2-week recovery: ----------monkeys----------, GLP, Conducted at ----------. 6354-122), 8/02, Lot No. PD-01-01 (from Lot ----------)

3. IDU-PC-011: Effect of repeat intravenous administration of recombinant human α-L-Iduronidase with and without canine serum albumin to ------ dogs (---------- No. 6354-130), GLP, Conducted at ----------, 1/02, Lot No. PD-01-01 (from Lot ----------.

4. IDU-PC-012: A one-day evaluation of the hemodynamic effects of the administration of Aldurazyme™ (laronidase for injection) to dogs during a 4-hour infusion. GLP, conducted by ----------No. R-032), 9/00, Lot nos. ----------

5. IDU-PC-013: Intravenous fertility and general reproduction toxicity study of alpha-L-Iduronidase in rats: GLP, Conducted by ---------- Protocol Number 907-008, Biomarin Study Number 01035, 8/02, Lots no. ---------- ----------

6. IDU-PC-014: Intravenous developmental toxicity study of alpha-L-Iduronidase in rats; GLP, Conducted by ----------No. 907-007; Biomarin Study Number: 01037, 8/02, Lots no. ----------

Review of Preclinical Toxicology Studies:

Acute Toxicity Studies

1. **IDU-PC-007: An acute intravenous toxicity study in rats:**
   Species: ----------rats
   Dose Levels: 0, 0.29, 0.58, 5.8 mg/kg
   Route Duration: single IV bolus, + kills on day 15.
   Methods: Clinical signs, BW, clinical pathology, gross & histopathology.
   Findings: No abnormalities in BWs, clinical pathology, organ weights. Incidental gross finding of single pale focus in liver in a male (5.8mg/kg group). Increase in number (but not incidence of sporadic findings of small foci of hepatocellular necrosis).

   The NOAEL was $\leq$ 0.58 mg/kg

2. **IDU-PC-012: A one-day evaluation of the hemodynamic effects of the administration of Aldurazyme™ (laronidase for injection) to dogs during a 4-hour infusion: General GLP adherence**
   Species: ---------- dogs (2 females)
   Dose Levels: 0.7 mg/kg, 3.9 mg/kg, 4.9 mg/kg
   Route Duration: IV x 2 approximately 4 hour infusion. Low and high doses in each animal after a 30 minute space (one high dose 3.9 mg/kg & one high dose 4.9 mg/kg).
   Methods: Cardiovascular (EKG, BP) monitoring, kill same day as treatment 30 minutes after high dose treatment.
   Findings: No treatment related abnormalities in EKG or HR.

   The NOAEL was $\leq$ 4.9 mg/kg

Multidose Toxicity Studies

1. **IDU-PC-009: 26-week intravenous infusion toxicity study with recombinant human a-L-Iduronidase in monkeys with a 2-week recovery: ---------- monkeys----------:**

Species: ---------- monkeys ----------
Dose Levels: 0, 0.166, 1.659, 16.588 (5/sex/group)
Route Duration: IV bolus (7 hour infusion) weekly for 26 weeks.
Methods: Clinical signs, BW, clinical pathology, gross & histopathology, ophthalmic examinations, antibody analysis, toxicokinetics.
Findings: Monkey (152259) developed hypersensitivity with edema around eyes and muzzle half way through the fourth dose. No treatment-related abnormalities in food consumptions, organ weights, sperm counts or morphology, gross, or histopathology. Decrease in BW of females in low and mid-dose (0.166, 1.659 mg/kg) at week 26, no effect in high dose group.
Clinical pathology- All monkeys in the high dose groups (male & female) 16.588 mg/kg have increased total leukocyte, lymphocytes and eosinophil counts, and monocyte counts (female) at one or more treatment groups. The changes (except eosinophil in male, and monocyte in female) resolved during the recovery period. No specific clinical sequelae of these changes were seen.
Antibody assays-
Approximately half the animals had increased levels of antibodies at 26 weeks versus the levels at 13 weeks. The animals that developed antibodies to rhIDU developed them to various levels (61.2-8843.9 A_{450} units per μL serum at week 26). The response does not appear to be dose related. There was no difference in antibody levels due to sex.
Pharmacokinetics- Serum rhIDU levels were insufficient at 0.166 mg/kg to perform pK analysis. Decreased AUC in 1.659 mg/kg group at 1, 13 and 26 weeks, but not seen at high dose (16.588 mg/kg). Liver levels of rhIDU determined and found to be dose-related.

The NOAEL was 1.659 mg/kg

2. **IDU-PC-011: Effect of repeat intravenous administration of recombinant human α-L-Iduronidase with and without canine serum albumin to ----- dogs:**
Species: ------ dog
Dose Levels: 0, 1.6 mg/kg
Route Duration: IV 4 hour infusion once a week for 8 weeks.
Methods: Clinical signs, BW.
Findings: All formulations induced facial edema, emesis, mucoid stools and/or

excessive salivation starting at the third dose. The severity of clinical effects were ranked thus: rhIDU> rhIDU with dog serum> rhIDU with Tween 80.

Reproductive/Developmental Toxicity Studies

1. **IDU-PC-013: Intravenous fertility and general reproduction toxicity study of alpha-L-Iduronidase in rats:**

Species: ----------rats (25/sex/group)

Dose Levels: 0, 0.036, 0.36, 3.6 mg/kg/day for rhIDU and 5mg/kg for diphenhydramine (DPH) pretreatment for all rhIDU doses including a vehicle control.

Route Duration: IV bolus for rhIDU and DPH. Male rats – rhIDU daily for 21 days prior to cohabitation for a total of 28 days (DPH days 9-35). Female rats – Daily rhIDU 15 days before cohabitation and until DG7 (DPH day 1 of study until DG7). Male sac at day after mating, female at DG 21.

Methods: Clinical signs, BW, food consumption, vaginal smears, sperm evaluation, gross & histopathology.

Findings: Female: Reduction of increase in weight in DPH, 0.036, 3.6 mg/kg groups for DS 8 to 15. No Rx-related biological effects on clin signs, food consumption, gross path, estrous cycles – normal. Male: Testes/prostate/seminal vesicles/epididymides wts - comparable between groups. No adverse effects on sperm motility, sperm counts, sperm morphology

Mating indices= 100%/100%/100%/100%/100% at 0/DPH (5)/0.036/0.36/3.60 mg/kg

Pregnancy rates = 96%/87.5%/92%/91.7%/88% at 0/DPH (5)/0.036/0.36/3.60 mg/kg

Mean percent preimplantation loss per rat [corpora lutea minus implants] = 12/10/12/17/10 at 0/DPH (5)/0.036/0.36/3.60 mg/kg

Mean percent postimplantation loss per rat [implants minus live fetuses] = 2.5/3.6/3.9/3.2/4.2 at 0/DPH (5)/0.036/0.36/3.60 mg/kg

Mean number of live fetuses per rat = 15.4/14.7/15/14/14.8 at 0/DPH(5)/0.036/0.36/3.60 mg/kg

2.**IDU-PC-014: Intravenous developmental toxicity study of alpha-L-Iduronidase in rats:**

Species: ---------- rats (25 female rats/group)

Dose Levels: 0, DPH (5), 0.036, 0.36, 3.6 mg/kg

Route Duration: Slow IV bolus daily on DGs 7 through 17.

Methods: Clinical signs, BWs, food consumption, vaginal smears, TK profile, pregnancy rate, uterine contents, ovary evaluation, gross evaluation, fetal exams

Findings: There were statistically significant reductions in body weight gains (DGs10-12) in the 0.36 and3.6 mg/kg/day groups and in the food consumption on days 15 to 18 in the 0.36 and 3.6 mg/kg groups. No adverse effects on clinical signs, estrous cycles, gross pathology

Mating indices= 100% - all groups

Pregnancy rates = 88%/96%/84%/96%/100% at 0/DPH (5)/0.036/0.36/3.6 mg/kg

Mean percent preimplantation loss per rat = 6.4%/6.3%/11%/8.3%/3.2% at 0/ DPH (5)/0.036/0.36/3.6 mg/kg

Mean percent postimplantation loss per rat = 3.2%/3.8%/2.9%/1.7%/2.4% at 0/ DPH (5)/0.036/0.36/3.6 mg/kg

Mean number of live fetuses per rat = 14.3/14/13.1/14.5/14.4 at 0/ DPH (5)/0.036/0.36/3.6 mg/kg

F1 Fetuses - No Rx-related effects on BWs, external, visceral, or skeletal anomalies

The NOEL was 0.036 mg/kg/day for parental toxicity and for fertility & reproductive performance. The NOEL for embryotoxicity was >3.6 mg/kg/day.

Mutagenicity Studies

No studies were performed.

Carcinogenicity Studies

No studies were performed.

Safety Pharmacology Studies

No studies were performed.

Conclusion

Aldurazyme™ is a highly purified and well-characterized 83 kD glycoprotein. It is isolated from cell culture supernatant after growth of CHO cells transfected with a recombinant expression vector encoded for rhIDU The proposed clinical indication is the long term enzyme replacement therapy in patients with Mucopolysaccharidosis I (MPS I; a-L-iduronidase deficiency) to treat the non-central nervous system manifestations of the disease. The safety, efficacy, pharmacokinetics and biodistribution of recombinant human a-L-iduronidase (rhIDU) have been evaluated using studies in four species (dog [MPS I and wild-type], MPS I cat, ---------- monkey, and ---- rat) of animals. The results of those studies demonstrate that rhIDU has an acceptable safety profile, with no consistent, treatment-related toxicity other than the immune reaction of the animals to a foreign protein and/or other constituent of the product. The most significant treatment-related finding seen in the preclinical studies was an anaphylactoid reaction that occurred in several dogs in early pharmacology studies. Reoccurrence of this event was prevented in most of the later studies by pharmacological pretreatment of the animals and changes in the dosing solution and regimen, however a significant infusion reaction occurred in the---------- monkey study during administration of the fourth dose. The animal had not been pretreated.

Two species (dog and cat) provide natural animal models of the MPS I disease, and a ---------- mouse model has been described (but not submitted in the BLA application)(Haskins 1997, He 1999, Clarke 1997). The naturally occurring feline MPS I model the disease is a result of a----------. The canine model is maintained in a mixed breed colony manifestations seen in naturally occurring disease is remarkably

similar in three species known to have natural disease, human, cat, and dog. The manifestations emanate from a marked deficiency of the lysosomal enzyme, α-L-iduronidase which is manifested universally by excessive urinary dermatan sulfate and heparan sulfate. The clinical features in all three species include facial dysmorphia, corneal clouding, cardiac valvular insufficiencies and bone disease. Felines affected by the disease do not manifest the growth delay that is a prominent feature in human and canine disease, but do survive to reproductive age, as do canines and humans. The sponsor has submitted seven studies in naturally occurring models of disease (six MPS I canine studies, one MPS I feline study) as pharmacodynamic studies to support the rationale of biological effectiveness in of the product, Aldurazyme™.

The MPS I canine studies submitted (IDU-PC-002, IDU-PC-003, IDU-PC-004, IDU-PC-005, IDU-PC-006, IDU-PC-008) are intravenous studies that explore dose and dosing regimens. The studies used a total of 28 dogs including controls. The consistent pharmacologic finding in these studies was that the treatment decreased GAG accumulations in the liver. This finding was seen across the 20U/kg/week to 100U/kg/week dose range and across various dosing regimens (single IV dosing, every other day dosing, and continuous infusions). Although longer duration studies (IDU-PC-005, IDU-PC-006) also reduce GAG accumulations in additional tissues such as kidney, spleen, adrenal gland, lymph nodes, small intestine, joint synovium, and gall bladder as measured by histology, histological evaluation failed to demonstrate a reduction in GAG accumulation in the CNS or in cartilage as measured by a reduction in vacuolation. Biochemically a reduction (62% in the cerebrum and 40% in the cerebellum) was demonstrated in IDU-PC-005 as compared to the untreated MPS I dogs.

The preclinical pharmacodynamic studies submitted in the IND suggest that enzyme replacement with rhIDU is effective in reducing the GAG accumulation in several soft tissues including the liver, spleen, lymph nodes, adrenal glands, small intestine, gall bladder and joint synovium in the both canine and feline MPS I disease models as determined by histology. However, the clinical significance of these histologic findings was not directly addressed in the studies and the lack of histologically significant changes in GAG accumulation in cartilage and the central nervous system suggest that the treatment may not prove effective against the orthopedic and cognitive manifestations of the clinical disease. The studies do not provide evidence that at the doses administered rhIDU is able to penetrate and accumulate to effective concentrations in cartilage and

central nervous system tissues, however the studies do not preclude the possibility that a higher dose or more frequent dosing regimen may produce enzyme concentrations sufficient to produce histologically significant changes in GAG accumulation in tissues that appear resistant to the short-term treatment. It should be noted that in addition to biochemical effects (increases in a-L-iduronidase activity levels in most tissues, decreases in GAG levels in tissues and urine, and histopathological evidence of tissue and organ improvement) demonstrated in the short term animal models long-term treatment of MPS I dogs (up to 74 weeks) with rhIDU resulted in improvement of clinical symptoms.

Subsequent formal toxicity studies in rats, dogs and monkeys further support the relative safety of rhIDU treatment. Of note there were only limited pharmacokinetic studies conducted and this topic should be addressed in more detail in post-marketing commitments. However the studies do suggest that the doses used in the clinical trial are sufficient to saturate a high affinity cellular receptor recognizing IDU. Acute toxicity studies were limited to a 15 day single dose IV study in the ----------rats and a single day repeat dose, dose escalation study in the ------. Neither study revealed toxicities. The primary toxicology study was a 26-week study in ---------- monkeys with 26 weekly IV bolus doses with a two-week recovery period. The highest dose used was 10 fold the dose used in the clinical trials. All monkeys in the high dose group had slightly elevated total leukocyte, lymphocytes, monocytes, and eosinophil counts that returned to normal levels after treatment (except eosinophils in males and monocytes in females). There was a single animal (152259) with a hypersensitivity reaction as described earlier in this section of the review. Approximately half of the monkeys developed anti-rhIDU antibodies. Neither the frequency nor the titer of the antibody was dose-related. The effect of the antibodies on pharmacokinetics was not well studied. Antibody production and pharmacokinetics can be further examined in phase IV studies. An eight-week repeat dose study was conducted to beagles to determine if changes in formulation effected the severity of infusion reactions. Although all the formulations tested exhibited infusion reactions after the third weekly dose the formulation incorporating Tween-80 produced the less severe reaction. Reproduction studies conducted in ----------rats failed to demonstrate deleterious effects on fertility, reproduction or development. In summary, the preclinical data adequately support use of the product, Aldurazyme^{TM}, for the indication specified by the sponsor.

_____ M. David Green Ph.D., Branch Chief

_____ Richard D. McFarland Ph.D., M.D., Medical Officer

Key Words; Hurler syndrome; Hurler-Scheie syndrome; Scheie Syndrome; Aldurazyme™; laronidase; mucopolysaccharidosis I; MPS I; α-L-iduronidase enzyme deficiency; lysosomes; lysosomal storage disease; antibodies; reproductive/developmental toxicity; non-human primate.

cc:

OTRR/DCTDA/CPT/MGreen

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5	**HomoloGene:** eukaryotic homology groups		1665	**Cancer Chromosomes:** cytogenetic databases	
none	**PubChem Compound:** small molecule chemical structures		none	**PubChem BioAssay:** bioactivity screens of chemical substances	
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE

VOLUME I

Tuesday, March 13, 2001

8:00 a.m.

Holiday Inn Gaithersburg
Two Montgomery Village Avenue
Gaithersburg, Maryland

PARTICIPANTS

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Sandra Titus, Executive Secretary

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Steven DeKosky, M.D.
Ranjan Duara, M.D.
Steven Ferris, M.D.
Mary Ganguli, M.D.
Ronald Petersen, M.D., Ph.D.

PUBLIC SPEAKERS:

Dr. Barry Reisberg
Dr. Tony Waegeman
Dr. Yogesh Shah

FDA:

Robert Temple, M.D.
Russell Katz, M.D.
Ranjit Mani, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. KAWAS: Good morning, and welcome to our meeting of the Peripheral and Central Nervous System Drug Advisory Committee. My name is Claudia Kawas. I am from the University of California at Irvine, and we will now call the meeting to order.

If we can begin first with introductions so everyone will know who is seated around the table, perhaps we can start with the FDA in the corner. Dr. Katz?

DR. KATZ: Russ Katz, Division of Neuropharmacological Drug Products at the agency.

DR. MANI: Ranjit Mani, Division of Neuropharm.

DR. PENIX: LaRoy Penix, Moorehouse School of Medicine, Neuroscience Institute.

DR. VAN BELLE: Gerald Van Belle, University of Washington in Seattle.

DR. WEINER: Howard Weiner, Brigham and Women's Hospital, Harvard Medical School.

DR. WOLINSKY: Jerry Wolinsky, University of Texas, Houston.

DR. GRUNDMAN: Michael Grundman, University of California, San Diego.

DR. TITUS: Sandy Titus, the FDA. I am the executive secretary for this committee.

DR. PETERSEN: Ron Petersen, Mayo Clinic, Rochester, Minnesota.

DR. GANGULI: Mary Ganguli, University of Pittsburgh.

DR. DUARA: Ranjan Duara, University of Miami School of Medicine.

DR. DEKOSKY: Steven DeKosky, University of Pittsburgh.

DR. FERRIS: Steven Ferris, New York University School of Medicine.

DR. KAWAS: Thank you very much. I think we have a very interesting day. We will now let Dr. Titus read the conflict of interest statement.

Conflict of Interest Statement

DR. TITUS: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting with the following exceptions:

Since the issue to be discussed by the committee at this meeting will not have a unique impact on any particular firm or product but, rather, may have widespread implications with respect to an entire class of products, in accordance with USC 208(b), each participant has been granted a waiver which permits them to participate in today's discussions.

A copy of these waiver statements may be obtained by submitting a written request to agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

With respect to FDA's invited guests, there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments. Dr. Ronald Petersen would like to disclose that he is project director on a National Institute of Aging grant which is supported by Pfizer, Eisai and Roche Vitamins.

Dr. Philip Gorelick would like to disclose that he has two NIH grants. Roche Laboratories and Bayer supplies the medication for each of these grants. In addition, he is on the speaker bureaus for Janssen/Excerpta Medica, Dupont, Roche Laboratories, Bristol Myers Squibb and Boehringer Ingelheim. Dr. Gorelick has consultant agreements with NPS, Eisai, G.D. Searle/Lorex, Roche Laboratories, Ketchum, AstraZeneca, Glaxo Wellcome, Warner-Lambert, Baxter, Rand, Solvay Pharmaceutical and Consumer Healthcare Products

Association. He is also on the Through Leader Panel which is supported by the Weinberg Group.

Dr. Ranjan Duara would like to disclose that he is an investigator on a study entitled Validations of a Memory Screening Instrument. The study is supported by a contract from Pfizer. He also serves as a scientific advisor for Pfizer/Eisai, Novartis and Janssen.

Dr. Steven DeKosky would like to report that he owns stock in Cephalon. He is a research investigator for Eisai-Pfizer, Novartis, and Schwabe. In addition, Dr. DeKosky consults for Pfizer, Cephalon, Schwabe, Janssen, Novartis, AstraZeneca and Eli Lilly, and serves as a speaker for Novartis.

Finally, Dr. Mary Ganguli would like to report that she is a researcher for the National Institutes of Health.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusions will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products

they may wish to comment upon. Thank you.

DR. KAWAS: Thank you, Dr. Titus. I think Dr. Temple just joined us. Maybe we can let him introduce himself.

DR. TEMPLE: I am Dr. Temple. I am director of this Office in which Neuropharm is.

DR. KAWAS: This committee was convened in order to discuss the topic of MCI or mild cognitive impairment. We have an awful lot of material that is going to be presented today by an awful lot of people. I am told I am supposed to be up here with a timer that has fifteen minutes for each of you to speak and five minutes of questions, and that is going to be the challenge of the day. There is a light up there for the speakers. You will have a two-minute warning when the light will become yellow. After that Sandy gets up on the table and starts making signs if you go beyond.

I wanted us to have a lot of time for discussion. So, we are going to try and keep the presentations as much on schedule as possible, realizing that some of the discussion might happen in the middle of presentations. By unanimous opinion and coercion, Dr. Ron Petersen has been moved into the first speaker slot. So, without further ado, Dr. Petersen, Mayo Clinic, Department of Neurology. Oh, we left out Dr. Katz.

[Laughter]

We really do want to give FDA their time to tell us our mission for today. So, Dr. Russell Katz?

Welcome and FDA Overview of Issues

DR. KATZ: First of all, good morning. I would like to welcome the committee to this meeting, the PCNS advisory committee. I would particularly like to extend an additional welcome to our invited guests who have agreed to graciously give their time and their expertise to help us out this morning. Let me also thank Sandy Titus for arranging the meeting, and I would particularly let me thank explicitly Dr. Ranjit Mani, a medical reviewer in the Division, who is sitting at the table, who really pretty much put the meeting together, identified the experts who are here today, invited them, and pretty much wrote the briefing memo in the books that you have received for today's and tomorrow's meeting. So, thanks, Ranjit.

We are actually presenting you with a fairly unusual problem today. Ordinarily we would bring to the committee a particular application for a new drug and we would ask you to interpret the data and help us out there, but today we are asking you a very different sort of question, a more difficult question, it seems to me. We are asking you to address some fundamental aspects of a particular diagnosis to help us characterize, decide if it

exists and how best it ought to be studied. That is unusual and we know it is difficult.

The reason we are asking now is because a number of pharmaceutical sponsors have approached the Division, asking to develop treatments for mild cognitive impairment or MCI. MCI, as you know, has been characterized variously in the literature but, in general, it is a condition that is described as occurring in elderly patients who predominantly have a memory impairment, some slight cognitive impairment perhaps and some minimal dysfunction in their daily functioning, although that is generally relatively intact, and patients are considered neither to be normal nor to have dementia but their cognitive status falls somewhere in between.

Most of the trials that the sponsors have come to us with have identified as a primary measure of drug effect time to progression to Alzheimer's disease, although some of them look strictly at the symptoms of MCI. We have let these trials proceed but we have told all sponsors that we will not make any commitments as far as interpreting the data pending a wider discussion of some of these more fundamental questions that I hope we will work out or at least discuss today.

By way of background, let me just say that the Federal Food, Drug and Cosmetic Act, which is the statute

under which we regulate drugs, requires that in order for a new drug to be approved the sponsor must submit what is called substantial evidence of effectiveness that the treatment will have the effect represented for it in product labeling. It is important to understand that a product's approval is inextricably linked to the language that is used in product labeling. I say this because one of the most critical factors that we need to consider when we are considering approving a drug and, therefore, writing labeling for it is whether or not the population for whom the drug is intended can be unambiguously described.

So, that takes us to the first question we would like you to think about. In the case of MCI there is not unanimity in the literature about the diagnostic criteria that can reliably identify patients who are alleged to have the condition. So, as I say, one of the critical questions we would like you to address is whether or not you believe that there do exist a set of criteria that can be readily applied by practitioners and that can reproducibly and reliably identify patients presumed to have MCI.

Ordinarily, diagnostic criteria are ideally compared to a gold standard to decide how specific and sensitive they are. Obviously, for example, in Alzheimer's disease the clinical criteria can be validated against the pathologic findings and they do pretty well, as you know,

against those. But, given the nature of MCI, there isn't this wide, robust pathologic database against which to compare the diagnostic criteria. So, that is a particular complication here.

Even if you find that there is a specific set of diagnostic criteria that can reliably identify patients as having MCI, there is another very critical question we would like you to address, and I guess it will take up a good part of the discussion this afternoon. In longitudinal studies of patients diagnosed with MCI, a substantial proportion of those patients go on to progress to frank Alzheimer's disease, and I expect that later today we will hear various estimates about the probability of that happening in these cohorts. In addition, static and functional imaging studies in patients diagnosed with MCI reveal changes that are basically qualitatively similar to those seen in Alzheimer's patients, though quantitatively much less severe, and the few pathologic studies that have been done in these patients also reveal qualitatively similar changes as those seen in patients with Alzheimer's disease.

These factors, taken together, suggest that MCI may, in fact, just simply be early Alzheimer's disease in patients who have not yet progressed to the point where they meet the formal, accepted clinical criteria for making that diagnosis. So, we are particularly interested in your views

on whether or not you think MCI really is just early Alzheimer's disease. It is critical because if it is early Alzheimer's disease it would be inappropriate to grant a claim for the indication of MCI when, in fact, it really is something else.

As you probably know, currently there are four approved treatments for Alzheimer's disease and for what we call mild to moderate Alzheimer's disease, and it is fair to ask if a drug is shown to be effective in patients diagnosed we MCI, if that is fundamentally different from the claims that we have already granted to these four drugs.

In fact, as I said earlier, the trial design that we have most commonly seen for these patients looks, as a primary measure of drug effectiveness, at time to diagnosis of Alzheimer's disease. So, that design itself could be taken to suggest that, in fact, these patients really just have an early stage of that condition.

It is also true that in the longitudinal studies which document progression to Alzheimer's disease in some proportion of patients that there is some proportion of patients who don't progress to Alzheimer's disease. That might possibly be an artifact of the fact that the follow-up in those studies was not long enough. I suppose if you follow long enough it is possible that all patients would progress to Alzheimer's disease but, nonetheless, the

Lipitor as a Treatment for Alzheimer's Disease

This study is no longer recruiting patients.

Sponsored by:	Institute for the Study of Aging Pfizer
Information provided by:	National Institute on Aging (NIA)

Purpose

The purpose of this study is to assess the clinical benefit of Lipitor, a cholesterol-lowering drug, in the treatment of Alzheimer's disease.

Condition	Treatment or Intervention	Phase
Alzheimer Disease	Drug: Atorvastatin calcium	Phase II

MedlinePlus related topics: Alzheimer's Caregivers; Alzheimer's Disease
Genetics Home Reference related topics: Alzheimer disease

Study Type: Interventional
Study Design: Treatment, Randomized, Double-Blind, Placebo Control, Efficacy Study

Official Title: Effect of the HMG-CoA Reductase Inhibitor Atorvastatin Calcium, Lipitor, in the Treatment of Alzheimer's Disease

Further Study Details:

Expected Total Enrollment: 98

Study start: October 2000; Study completion: April 2004
Last follow-up: August 2004

This study is a phase II, placebo controlled, double-blind, one year trial investigating the effect of HmG-CoA reductase inhibitor atorvastatin calcium in the treatment of persons with possible or probable Alzheimer's disease. Subjects may continue to take stable doses of Aricept and Exelon. Following enrollment, participants will make visits to the study center every three months for blood tests and neuropsychological testing.

Eligibility

Ages Eligible for Study: 50 Years and above, Genders Eligible for Study: Both

Criteria

FDA Talk Paper

T04-09
April 21, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

***** CLARIFICATION *****
Paragraph three revised 04/26/2004.

FDA Approves Apokyn for the Acute Treatment of Episodes of Immobility in Parkinson's Patients

FDA has approved Apokyn (apomorphine) as an injectable drug for treating Parkinson's patients during episodes of "hypomobility," so-called "off periods" in which the patient becomes immobile or unable to perform activities of daily living. Apokyn was given priority review because injectable apomorphine is the first therapy approved to treat these episodes acutely (during the episode). Apokyn was also designated as an orphan product.

An estimated 1.5 million Americans have Parkinson's disease, which results in tremors, rigidity, postural instability, slowness, and difficulty moving.

Within 3 to 5 years of treatment with standard Parkinson's drug treatments, many patients experience episodes of hypomobility (e.g., inability to rise from a chair, to speak, or to walk). The episodes can occur toward the end of a dosing interval with standard background medications (so-called "end-of-dose wearing off") or at unpredictable times (spontaneous "on/off"). Approximately 10 percent of Parkinson's patients who are unresponsive to standard medications may benefit from Apokyn.

Apokyn was designated an orphan drug in 1991 to treat the ten percent, or about 112,000 Parkinson's patients who progress to stage four and experience the severe on/off motor fluctuations unresponsive to other therapies. Orphan drugs are drugs that treat a rare disease or condition which affects fewer than 200,000 patients in the U.S. After receiving FDA approval, orphan drugs are eligible for seven years of exclusive marketing.

The effectiveness of Apokyn in the acute symptomatic treatment of both types of recurring episodes of hypomobility or "off" episodes associated with advanced Parkinson's disease was established in three randomized, controlled trials. On average, patients participating in these trials had had Parkinson's disease for 11.3 years and were being treated with L-dopa and at least one other agent, usually an oral dopamine agonist.

Apokyn must be taken with an antiemetic drug because, when taken alone, it causes severe nausea and vomiting. It must not be taken with one class of very effective anti-nausea drugs, the 5HT3 antagonists (ondansetron and similar drugs), because the combination of Apokyn (apomorphine) and these drugs can lead to very low blood pressure and loss of consciousness.

Apokyn is intended for subcutaneous injection only. Other oral drugs, taken chronically, are also used to help decrease the amount of time Parkinson's patients spend in the "off" state.

DGNews

FDA Approves Namenda (Memant HCl) for Treatment of Moderate to S Alzheimer's Disease

NEW YORK, NY -- October 17, 2003 -- Forest Laboratorie (NYSE: FRX) announced today that Namenda™ (memantir first of a new class of drugs for Alzheimer's disease, was ap the U.S. Food and Drug Administration (FDA) for the treati moderate to severe Alzheimer's disease. Forest expects Nan available to physicians, patients, and pharmacies in January Namenda is the first NMDA receptor antagonist to be appro Alzheimer's disease and is also the only therapy approved f treatment of moderate to severe Alzheimer's disease.

"The approval of Namenda offers an important new therape for patients suffering from moderate to severe Alzheimer's d Howard Solomon, Chairman and Chief Executive Officer o Laboratories. "Previously patients with moderate disease ha class of options; now they have an additional therapy availa patients who had progressed beyond the moderate stage of A disease had no approved therapeutic option at all. We believ will provide a meaningful benefit to millions of Americans from Alzheimer's disease, whether as a patient, caregiver, o member."

Namenda will be available in pharmacies in January 2004. I

Recent news - Alzheimer's

- Aricept Appears to Demonstrate Significant Treatment Benefits in Patients Exclusively With Early-Stage Alzheimer's Disease - *(DGNews)*
- Rate Of Decline In Cognitive Functioning Similar In Patients With Parkinson Disease and Dementia and Patients With Alzheimer Disease - *(DGNews)*
- Health Canada Approves Ebixa (Memantine) for Treatment of Moderate-to-Severe Alzheimer's Disease - *(DGNews)*

Note:

These press releases and statements were accurate, in all material respects, at the time of their issuance. However, Johnson & Johnson and the operating companies assume no obligation to update, correct or otherwise modify any of this material. We recommend that you view the most recent press releases and statements in order to receive the most current information made available by Johnson & Johnson.

REMINYL®, New Treatment For Alzheimer's Disease, Receives FDA Approval

REMINYL® Derived from the Daffodil

Titusville, NJ (February 28, 2001) – REMINYL® (galantamine hydrobromide) – a new treatment for mild to moderate Alzheimer's disease derived from the bulbs of daffodils – was approved today by the U.S. Food and Drug Administration (FDA).

Data from four placebo-controlled, double-blind clinical trials involving more than 2,650 patients show that REMINYL® can have a beneficial effect on patients' daily function and ability to think. To be available by prescription in May, REMINYL® was developed by the Janssen Research Foundation under a co-development and licensing agreement with the UK-based Shire Pharmaceuticals Group plc.

An estimated four million Americans have Alzheimer's disease – a progressive loss of cognitive function (thinking, remembering and reasoning) so severe that it interferes with an individual's ability to function. That number is expected to grow to 14 million by the middle of the next ce disorder is the third-most-expensive illness in the United States, behind on disease and cancer.

"Alzheimer's disease patients progressively deteriorate," says Gary Small, I of the Center on Aging and professor of psychiatry and biobehavioral scien University of California in Los Angeles. "But the studies show that REMINYL benefit many individuals with the disease. In studies lasting up to six mont patients' symptoms initially improved or stabilized, and even when they be decline, they remained better than those who were treated with placebo."

In studies ranging from 12 to 26 weeks, the effectiveness of REMINYL® wa using two primary tools. Patients' abilities related to memory, orientation, and language were assessed using the cognitive portion of the Alzheimer's Assessment Scale (ADAS-cog). Across all studies, the results consistently demonstrated that more patients taking REMINYL® showed significant imp their cognitive performance than those receiving placebo (inactive medicati

The second primary measure of effectiveness was the Clinician's Interview-Impression of Change plus Caregiver Information (CIBIC-plus), which prov overall assessment of patient functioning, including behavior, organized th

Archive

- Ortho-McNeil Ph Inc., Receives S TOPAMAX® (December 12,
- Study Suggests CONSTA™, Nev For Schizophrer Further Relieve Stable Patients (December 10,
- ALZA Corporati 48 Filing (December 9, 2
- Holiday Break I Creates Challen Children, Careg (December 9, 2
- Treating Schizo Patients With R CONSTA™ May Hospitalization Cost of Care (December 9, 2
- FDA Approves I for Treatment c Mania (December 5, 2
- More News

Drugs Approved by the FDA

Drug Name: Exelon (rivastigmine tartrate)

The following information is obtained from various newswires, published medical journal articles, and medical conference presentations.

Company: Novartis
Approval Status: Approved April 2000
Treatment for: Indicated for the treatment of mild to moderate dementia of the Alzheimer's type

General Information

Exelon has been approved in oral solution *and* capsule form for the treatment of mild to moderate Alzheimer's disease. This drug belongs to the class of drugs called cholinesterase inhibitors. Cholinesterase breaks down acetylcholine, a neurotransmitter which assists in human memory and cognition processes. By inhibiting cholinesterase, more acetylcholine available to the patient for memory and cognitive functioning. This is effective in treatment of Alzheimer's disease, since acetylcholine is at significantly lower levels in Alzheimer's patients than in normally functioning people.

Exelon has been shown to improve patients' performance in the three major domains of assessment of Alzheimer's: global functioning (such as activities of daily living), behavior, and cognition.

Another long term advantage to the drug is that it could treat symptoms early on in the deterioration process. Delaying the onset of the disease by five years in patients could save up to $50 billion in U.S. healthcare costs annually (half of the current annual cost).

Currently, 70 countries have approved Exelon for marketing.

Alzheimer's Disease is a neurodegenerative disease affecting up to 4 million adults in the U.S. and 10 million worldwide. Memory loss and other cognitive and behavior deteriorations are symptoms of the disease. As there is no current cure, Alzheimer's Disease is fatal.

Clinical Results

The safety and efficacy of Exelon was investigated in two placebo-controlled

FAQ's

Description of Medical Areas

About the FDA Approved Listings

Drugs Approved by the FDA

Drug Name: ARICEPT (donepezil hydrochloride)

The following information is obtained from various newswires, published medical journal articles, and medical conference presentations.

Company: Eisai
Approval Status: Approved December 1996
Treatment for: Alzheimer's Disease

General Information

Aricept has been approved for the symptomatic treatment of mild to moderate Alzheimer's disease. Aricept is effective in improving cognition and patient function in people with mild to moderate Alzheimer's Disease.

Clinical Results

Controlled clinical trials in over 900 subjects demonstrated that more than 80% of subjects taking Aricept either improved or exhibited no further demonstration in tests of cognition over the course of the studies. In an assessment of patient function, which includes general function, cognition, behavior and activities of daily living, clinicians rated approximately two times as many subjects on Aricept as improved in comparison to placebo after 24 weeks of treatment.

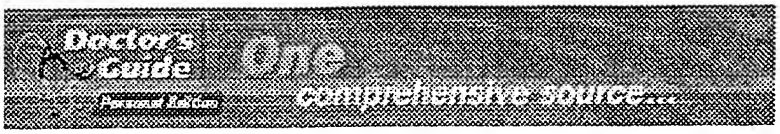
Mechanism of Action

Aricept is a new reversible inhibitor of the enzyme acetylcholinesterase. Acetylcholinesterase is an enzyme, which breaks down the neurotransmitter acetylcholine. Aricept may allow a greater concentration of acetylcholine in the brain, thereby improving cholinergic function. Acetylcholine, associated with memory and learning, is in short supply in subjects with Alzheimer's disease.

Drug listing last updated on June 29, 2004

PAC> 022660

CenterWatch Newly Approved Drug Therapies Listing



Comtan Receives FDA Approval For Manage Parkinson's Disease

EAST HANOVER, N.J. -- October 20, 1999 -- Comtan (entacapone), a new medication for Parkinson's Disea received marketing approval from the U.S. Food and D Administration (FDA).

Worldwide clinical studies and marketing experience ir approximately 30,000 patients have demonstrated thai enhances the benefits of levodopa in patients with Par who experience end-of-dose "wearing off". Comtan is approved for marketing in more than 35 countries.

"Comtan is an important new treatment in the manage Parkinson's Disease because it can help improve mot performance and significantly increase the amount of patients by prolonging the benefits of levodopa/carbidc preparations, the mainstay therapy," said Dr. Lynn Kra President, Nervous System, Clinical Research and De Novartis Pharmaceuticals Corporation. 'On' time refers of relatively good function, marked by patients' ability t common but important daily activities such as walking, writing and dressing. 'Off' time is characterized by peri immobility and a time when patients with Parkinson's a incapable of independent movement.

Optimizing Standard Parkinson's Disease Treatment

Comtan belongs to a new therapeutic class called COI inhibitors that block the COMT enzyme, and thus, redu breakdown of levodopa before it reaches the brain. Th of a COMT inhibitor to the treatment regimen ensures use of the prescribed levodopa/carbidopa, resulting in more sustained availability of levodopa for brain entry extending the positive effect of each levodopa dose. C exposure to dopamine allows patients to function more independently and for longer periods of time between

NOVARTIS

T2000-11
89007401

Exelon®

(rivastigmine tartrate)

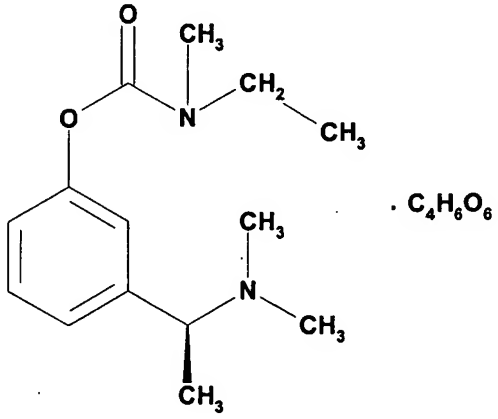
Capsules

Rx Only

Prescribing Information

DESCRIPTION

Exelon® (rivastigmine tartrate) is a reversible cholinesterase inhibitor and is known chemically as (S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]-phenyl carbamate hydrogen-(2R,3R)-tartrate. Rivastigmine tartrate is commonly referred to in the pharmacological literature as SDZ ENA 713 or ENA 713. It has an empirical formula of $C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6$ (hydrogen tartrate salt – hta salt) and a molecular weight of 400.43 (hta salt). Rivastigmine tartrate is a white to off-white, fine crystalline powder that is very soluble in water, soluble in ethanol and acetonitrile, slightly soluble in n-octanol and very slightly soluble in ethyl acetate. The distribution coefficient at 37°C in n-octanol/phosphate buffer solution pH 7 is 3.0.



Exelon is supplied as capsules containing rivastigmine tartrate, equivalent to 1.5, 3.0, 4.5 and 6.0 mg of rivastigmine base for oral administration. Inactive ingredients are hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, and silicone dioxide. Each hard-gelatin capsule contains gelatin, titanium dioxide and red and/or yellow iron oxides.

CLINICAL PHARMACOLOGY

Mechanism of Action

Pathological changes in Dementia of the Alzheimer type involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. These pathways are thought to be intricately involved in memory, attention, learning, and other cognitive processes. While the precise mechanism of rivastigmine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this proposed mechanism is correct, Exelon's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that rivastigmine alters the course of the underlying dementing process. After a 6-mg

dose of rivastigmine, anticholinesterase activity is present in CSF for about 10 hours, with a maximum inhibition of about 60% five hours after dosing.

Clinical Trial Data

The effectiveness of Exelon® (rivastigmine tartrate) as a treatment for Alzheimer's Disease is demonstrated by the results of two randomized, double-blind, placebo-controlled clinical investigations in patients with Alzheimer's Disease [diagnosed by NINCDS-ADRDA and DSM-IV criteria, Mini-Mental State Examination (MMSE) ≥10 and ≤26, and the Global Deterioration Scale (GDS)]. The mean age of patients participating in Exelon trials was 73 years with a range of 41-95. Approximately 59% of patients were women and 41% were men. The racial distribution was Caucasian 87%, Black 4% and Other races 9%.

Study Outcome Measures: In each study, the effectiveness of Exelon was evaluated using a dual outcome assessment strategy.

The ability of Exelon to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's Disease patients. The ADAS-cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis. The ADAS-cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment. Elderly normal adults may score as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher.

The patients recruited as participants in each study had mean scores on ADAS-cog of approximately 23 units, with a range from 1 to 61. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's Disease suggest that they gain 6-12 units a year on the ADAS-cog. Lesser degrees of change, however, are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in Exelon trials was approximately 3-8 units per year.

The ability of Exelon to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC-Plus. The CIBIC-Plus is not a single instrument and is not a standardized instrument like the ADAS-cog. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC-Plus reflect clinical experience from the trial or trials in which it was used and can not be compared directly with the results of CIBIC-Plus evaluations from other clinical trials. The CIBIC-Plus used in the Exelon trials was a structured instrument based on a comprehensive evaluation at baseline and subsequent time-points of three domains: patient cognition, behavior and functioning, including assessment of activities of daily living. It represents the assessment of a skilled clinician using validated scales based on his/her observation at interviews conducted separately with the patient and the caregiver familiar with the behavior of the patient over the interval rated. The CIBIC-Plus is scored as a seven point categorical rating, ranging from a score of 1, indicating "markedly improved," to a score of 4, indicating "no change" to a score of 7, indicating "marked worsening." The CIBIC-Plus has not been systematically compared directly to assessments not using information from caregivers (CIBIC) or other global methods.

U.S. Twenty-Six-Week Study

In a study of 26 weeks duration, 699 patients were randomized to either a dose range of 1-4 mg or 6-12 mg of Exelon per day or to placebo, each given in divided doses. The 26-week study was divided into a

12-week forced dose titration phase and a 14-week maintenance phase. The patients in the active treatment arms of the study were maintained at their highest tolerated dose within the respective range.

Effects on the ADAS-cog: Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the Exelon-treated patients compared to the patients on placebo were 1.9 and 4.9 units for the 1-4 mg and 6-12 mg treatments, respectively. Both treatments were statistically significantly superior to placebo and the 6-12 mg/day range was significantly superior to the 1-4 mg/day range.

Figure 1: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

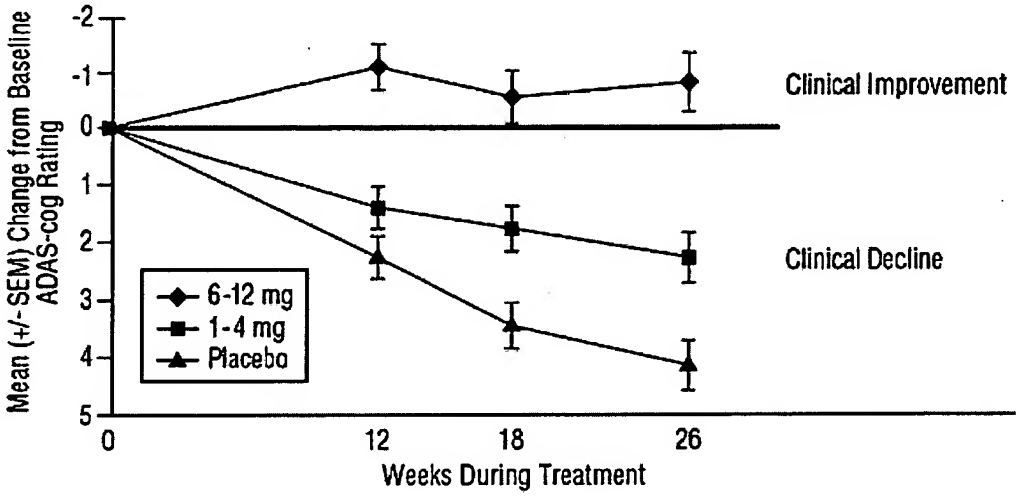
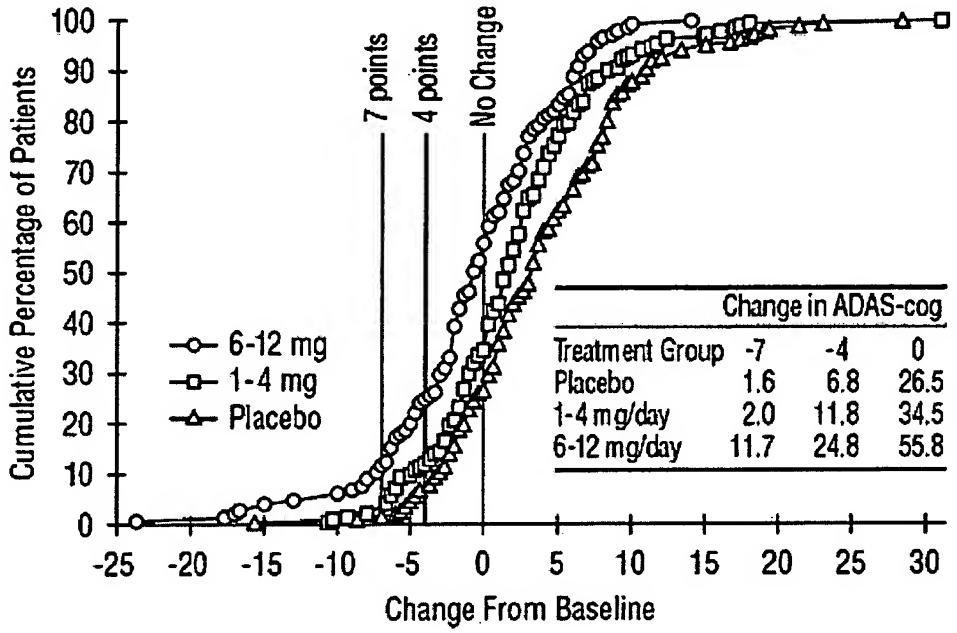


Figure 2 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Three change scores, (7-point and 4-point reductions from baseline or no change in score) have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

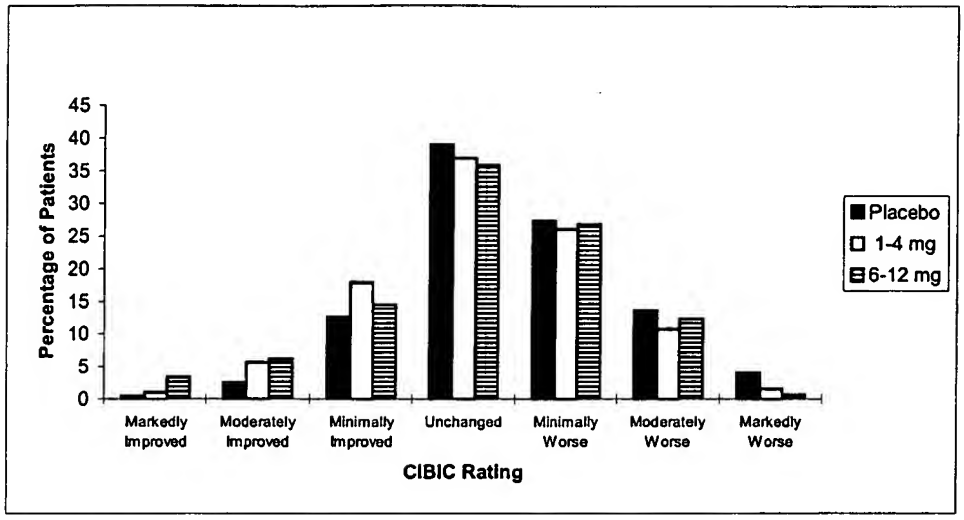
The curves demonstrate that both patients assigned to Exelon and placebo have a wide range of responses, but that the Exelon groups are more likely to show the greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon, or shifted to the right of the curve for placebo, respectively.

Figure 2: Cumulative Percentage of Patients Completing 26 Weeks of Double-blind Treatment with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 84%, 1-4 mg 85%, and 6-12 mg 65%.



Effects on the CIBIC-Plus: Figure 3 is a histogram of the frequency distribution of CIBIC-Plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean Exelon-placebo differences for these groups of patients in the mean rating of change from baseline were 0.32 units and 0.35 units for 1-4 mg and 6-12 mg of Exelon, respectively. The mean ratings for the 6-12 mg/day and 1-4 mg/day groups were statistically significantly superior to placebo. The differences between the 6-12 mg/day and the 1-4 mg/day groups were statistically significant.

Figure 3: Frequency Distribution of CIBIC-Plus Scores at Week 26



Global Twenty-Six-Week Study

In a second study of 26 weeks duration, 725 patients were randomized to either a dose range of 1-4 mg or 6-12 mg of Exelon per day or to placebo, each given in divided doses. The 26-week study was divided into a 12-week forced dose titration phase and a 14-week maintenance phase. The patients in the active treatment arms of the study were maintained at their highest tolerated dose within the respective range.

Effects on the ADAS-cog: Figure 4 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the Exelon-treated patients compared to the patients on placebo were 0.2 and 2.6 units for the 1-4 mg and 6-12 mg treatments, respectively. The 6-12 mg/day group was statistically significantly superior to placebo, as well as to the 1-4 mg/day group. The difference between the 1-4 mg/day group and placebo was not statistically significant.

Figure 4: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

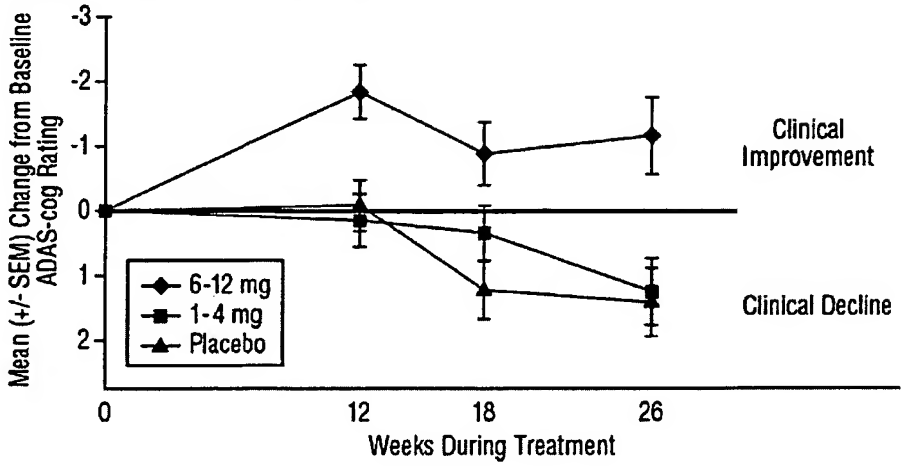
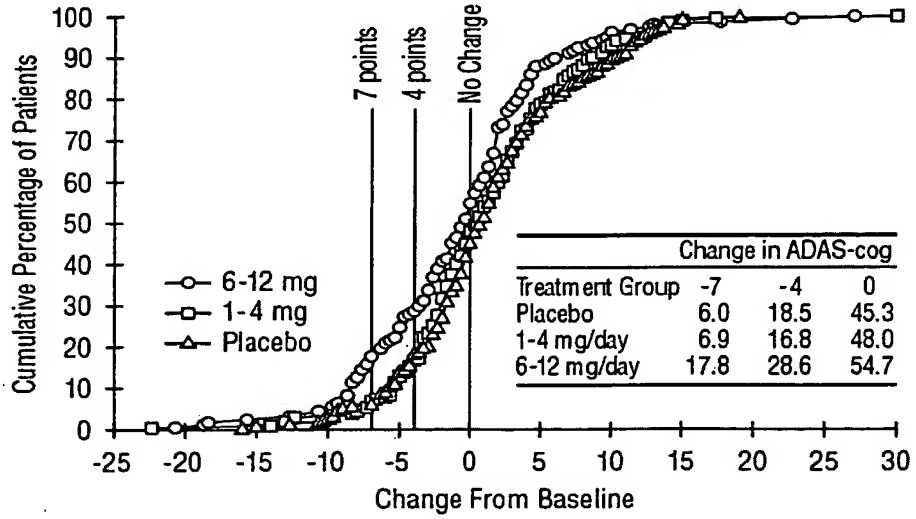


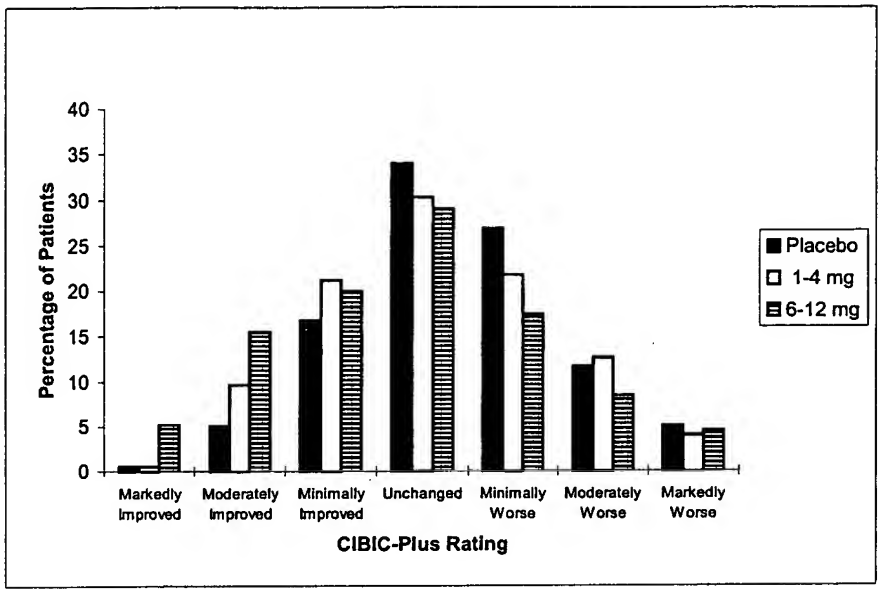
Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Similar to the U.S. 26-week study, the curves demonstrate that both patients assigned to Exelon and placebo have a wide range of responses, but that the 6-12 mg/day Exelon group is more likely to show the greater improvements.

Figure 5: Cumulative Percentage of Patients Completing 26 Weeks of Double-blind Treatment with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 87%, 1-4 mg 86%, and 6-12 mg 67%.



Effects on the CIBIC-Plus: Figure 6 is a histogram of the frequency distribution of CIBIC-Plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean Exelon-placebo differences for these groups of patients for the mean rating of change from baseline were 0.14 units and 0.41 units for 1-4 mg and 6-12 mg of Exelon, respectively. The mean ratings for the 6-12 mg/day group was statistically significantly superior to placebo. The comparison of the mean ratings for the 1-4 mg/day group and placebo group was not statistically significant.

Figure 6: Frequency Distribution of CIBIC-Plus Scores at Week 26



U.S. Fixed Dose Study

In a study of 26 weeks' duration, 702 patients were randomized to doses of 3, 6, or 9 mg/day of Exelon or to placebo, each given in divided doses. The fixed-dose study design, which included a 12-week forced titration phase and a 14-week maintenance phase, led to a high dropout rate in the 9 mg/day group because of poor tolerability. At 26 weeks of treatment, significant differences were observed for the ADAS-cog mean change from baseline for the 9 mg/day and 6 mg/day groups, compared to placebo. No significant differences were observed between any of the Exelon dose groups and placebo for the analysis of the CIBIC-Plus mean rating of change. Although no significant differences were observed between Exelon treatment groups, there was a trend toward numerical superiority with higher doses.

Age, Gender and Race: Patient's age, gender, or race did not predict clinical outcome to Exelon treatment.

Pharmacokinetics

Rivastigmine is well absorbed with absolute bioavailability of about 40% (3-mg dose). It shows linear pharmacokinetics up to 3 mg BID but is non-linear at higher doses. Doubling the dose from 3 to 6 mg BID results in a 3-fold increase in AUC. The elimination half-life is about 1.5 hours, with most elimination as metabolites via the urine.

Absorption: Rivastigmine is rapidly and completely absorbed. Peak plasma concentrations are reached in approximately 1 hour. Absolute bioavailability after a 3-mg dose is about 36%. Administration of Exelon with food delays absorption (t_{max}) by 90 min, lowers C_{max} by approximately 30% and increases AUC by approximately 30%.

Distribution: Rivastigmine is widely distributed throughout the body with a volume of distribution in the range of 1.8-2.7 L/kg. Rivastigmine penetrates the blood brain barrier, reaching CSF peak concentrations in 1.4-2.6 hours. Mean $AUC_{1\text{-}12hr}$ ratio of CSF/plasma averaged 40 ± 0.5% following 1-6 mg BID doses.

Rivastigmine is about 40% bound to plasma proteins at concentrations of 1-400 ng/mL, which cover the therapeutic concentration range. Rivastigmine distributes equally between blood and plasma with a blood-to-plasma partition ratio of 0.9 at concentrations ranging from 1-400 ng/mL.

Metabolism: Rivastigmine is rapidly and extensively metabolized, primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. Based on evidence from *in vitro* and animal studies the major cytochrome P450 isozymes are minimally involved in rivastigmine metabolism. Consistent with these observations is the finding that no drug interactions related to cytochrome P450 have been observed in humans [see Drug-Drug Interactions].

Elimination: The major pathway of elimination is via the kidneys. Following administration of ^{14}C-rivastigmine to 6 healthy volunteers total recovery of radioactivity over 120 hours was 97% in urine and 0.4% in feces. No parent drug was detected in urine. The sulfate conjugate of the decarbamylated metabolite is the major component excreted in urine and represents 40% of the dose. Mean oral clearance of rivastigmine is 1.8 ± 0.6 L/min after 6 mg BID.

Special Populations

Hepatic Disease: Following a single 3-mg dose, mean oral clearance of rivastigmine was 60% lower in hepatically impaired patients (n=10, biopsy proven) than in healthy subjects (n=10). After multiple 6 mg BID oral dosing, the mean clearance of rivastigmine was 65% lower in mild (n=7, Child-Pugh score 5-6) and moderate (n=3, Child-Pugh score 7-9) hepatically impaired patients (biopsy proven, liver cirrhosis) than in healthy subjects (n=10). Dosage adjustment is not necessary in hepatically impaired patients as the dose of drug is individually titrated to tolerability.

Renal Disease: Following a single 3-mg dose, mean oral clearance of rivastigmine is 64% lower in moderately impaired renal patients (n=8, GFR=10-50 mL/min) than in healthy subjects (n=10, GFR≥60 mL/min); Cl/F=1.7 L/min (cv=45%) and 4.8 L/min (cv=80%), respectively. In severely impaired renal patients (n=8, GFR<10mL/min), mean oral clearance of rivastigmine is 43% higher than in healthy subjects (n=10, GFR≥60 mL/min); Cl/F = 6.9 L/min and 4.8 L/min, respectively. For unexplained reasons, the severely impaired renal patients had a higher clearance of rivastigmine than moderately impaired patients. However, dosage adjustment may not be necessary in renally impaired patients as the dose of the drug is individually titrated to tolerability.

Age: Following a single 2.5 mg oral dose to elderly volunteers (>60 years of age, n=24) and younger volunteers (n=24), mean oral clearance of rivastigmine was 30% lower in elderly (7 L/min) than in younger subjects (10 L/min).

Gender and Race: No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of Exelon, but a population pharmacokinetic analysis indicates that gender (n=277 males and 348 females) and race (n=575 white, 34 black, 4 Asian, and 12 other) did not affect the clearance of Exelon.

Nicotine Use: Population PK analysis showed that nicotine use increases the oral clearance of rivastigmine by 23% (n=75 Smokers and 549 Nonsmokers).

Drug-Drug Interactions

Effect of Exelon on the Metabolism of Other Drugs: Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on *in vitro* studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.

No pharmacokinetic interaction was observed between rivastigmine and digoxin, warfarin, diazepam, or fluoxetine in studies in healthy volunteers. The elevation of prothrombin time induced by warfarin is not affected by administration of Exelon.

Effect of Other Drugs on the Metabolism of Exelon: Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine. Single dose pharmacokinetic studies demonstrated that the metabolism of rivastigmine is not significantly affected by concurrent administration of digoxin, warfarin, diazepam, or fluoxetine.

Population PK analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72), β-blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), non-steroidal anti-inflammatory drugs (n=79), estrogens (n=70), salicylate analgesics (n=177), antianginals (n=35), and antihistamines (n=15). In addition, in clinical trials, no increased risk of clinically relevant untoward effects was observed in patients treated concomitantly with Exelon and these agents.

INDICATIONS AND USAGE

Exelon® (rivastigmine tartrate) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRAINDICATIONS

Exelon® (rivastigmine tartrate) is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives or other components of the formulation (see DESCRIPTION).

WARNINGS

Gastrointestinal Adverse Reactions

Exelon® (rivastigmine tartrate) use is associated with significant gastrointestinal adverse reactions, including nausea and vomiting, anorexia, and weight loss. For this reason, patients should always be started at a dose of 1.5 mg BID and titrated to their maintenance dose. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose (see Dosage and Administration) to reduce the possibility of severe vomiting and its potentially serious sequelae (e.g., there has been one post-marketing report of severe vomiting with esophageal rupture following inappropriate reinitiation of treatment with a 4.5 mg dose after 8 weeks of treatment interruption.)

Nausea and Vomiting: **In the controlled clinical trials, 47% of the patients treated with an Exelon dose in the therapeutic range of 6-12 mg/day (n=1189) developed nausea (compared with 12% in placebo). A total of 31% of Exelon-treated patients developed at least one episode of vomiting (compared with 6% for placebo). The rate of vomiting was higher during the titration phase (24% vs. 3% for placebo) than in the maintenance phase (14% vs. 3% for placebo). The rates were higher in women than men. Five percent of patients discontinued for vomiting, compared to less than 1% for patients on placebo. Vomiting was severe in 2% of Exelon-treated patients and was rated as mild or moderate each in 14% of patients. The rate of nausea was higher during the titration phase (43% vs. 9% for placebo) than in the maintenance phase (17% vs. 4% for placebo).**

Weight Loss: **In the controlled trials, approximately 26% of women on high doses of Exelon (greater than 9 mg/day) had weight loss of equal to or greater than 7% of their baseline weight compared to 6% in the placebo-treated patients. About 18% of the males in the high dose group experienced a similar degree of weight loss compared to 4% in placebo-treated patients. It is not**

clear how much of the weight loss was associated with anorexia, nausea, vomiting, and the diarrhea associated with the drug.

Anorexia: In the controlled clinical trials, of the patients treated with an Exelon dose of 6-12 mg/day, 17% developed anorexia compared to 3% of the placebo patients. Neither the time course or the severity of the anorexia is known.

Peptic Ulcers/Gastrointestinal Bleeding: Because of their pharmacological action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of Exelon have shown no significant increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Anesthesia

Exelon as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Cardiovascular Conditions

Drugs that increase cholinergic activity may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. In clinical trials, Exelon was not associated with any increased incidence of cardiovascular adverse events, heart rate or blood pressure changes, or ECG abnormalities. Syncopal episodes have been reported in 3% of patients receiving 6–12 mg/day of Exelon, compared to 2% of placebo patients.

Genitourinary

Although this was not observed in clinical trials of Exelon, drugs that increase cholinergic activity may cause urinary obstruction.

Neurological Conditions

Seizures: Drugs that increase cholinergic activity are believed to have some potential for causing seizures. However, seizure activity also may be a manifestation of Alzheimer's Disease.

Pulmonary Conditions

Like other drugs that increase cholinergic activity, Exelon should be used with care in patients with a history of asthma or obstructive pulmonary disease.

PRECAUTIONS

Information for Patients and Caregivers

Caregivers should be advised of the high incidence of nausea and vomiting associated with the use of the drug along with the possibility of anorexia and weight loss. Caregivers should be encouraged to monitor for these adverse events and inform the physician if they occur. It is critical to inform caregivers that if therapy has been interrupted for more than several days, the next dose should not be administered until they have discussed this with the physician.

Drug-Drug Interactions

Effect of Exelon® (rivastigmine tartrate) on the Metabolism of Other Drugs: Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on *in vitro* studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.

No pharmacokinetic interaction was observed between rivastigmine and digoxin, warfarin, diazepam, or fluoxetine in studies in healthy volunteers. The elevation of prothrombin time induced by warfarin is not affected by administration of Exelon.

Effect of Other Drugs on the Metabolism of Exelon: Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine. Single dose pharmacokinetic studies demonstrated that the metabolism of rivastigmine is not significantly affected by concurrent administration of digoxin, warfarin, diazepam, or fluoxetine.

Population PK analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72), β-blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), nonsteroidal anti-inflammatory drugs (n=79), estrogens (n=70), salicylate analgesics (n=177), antianginals (n=35), and antihistamines (n=15).

Use with Anticholinergics: Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

Use with Cholinomimetics and Other Cholinesterase Inhibitors: A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In carcinogenicity studies conducted at dose levels up to 1.1 mg-base/kg/day in rats and 1.6 mg-base/kg/day in mice, rivastigmine was not carcinogenic. These dose levels are approximately 0.9 times and 0.7 times the maximum recommended human daily dose of 12 mg per day on a mg/m^2 basis.

Rivastigmine was clastogenic in two *in vitro* assays in the presence, but not the absence, of metabolic activation. It caused structural chromosomal aberrations in V79 Chinese hamster lung cells and both structural and numerical (polyploidy) chromosomal aberrations in human peripheral blood lymphocytes. Rivastigmine was not genotoxic in three *in vitro* assays: the Ames test, the unscheduled DNA synthesis (UDS) test in rat hepatocytes (a test for induction of DNA repair synthesis), and the HGPRT test in V79 Chinese hamster cells. Rivastigmine was not clastogenic in the *in vivo* mouse micronucleus test.

Rivastigmine had no effect on fertility or reproductive performance in the rat at dose levels up to 1.1 mg-base/kg/day. This dose is approximately 0.9 times the maximum recommended human daily dose of 12 mg/per day on a mg/m^2 basis.

Pregnancy

Pregnancy Category B: Reproduction studies conducted in pregnant rats at doses up to 2.3 mg-base/kg/day (approximately 2 times the maximum recommended human dose on a mg/m^2 basis) and in pregnant rabbits at doses up to 2.3 mg-base/kg/day (approximately 4 times the maximum recommended human dose on a mg/m^2 basis) revealed no evidence of teratogenicity. Studies in rats showed slightly decreased fetal/pup

weights, usually at doses causing some maternal toxicity; decreased weights were seen at doses which were several fold lower than the maximum recommended human dose on a mg/m^2 basis. There are no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Exelon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether rivastigmine is excreted in human breast milk. Exelon has no indication for use in nursing mothers.

Pediatric Use

There are no adequate and well-controlled trials documenting the safety and efficacy of Exelon in any illness occurring in children.

ADVERSE REACTIONS

Adverse Events Leading to Discontinuation

The rate of discontinuation due to adverse events in controlled clinical trials of Exelon® (rivastigmine tartrate) was 15% for patients receiving 6-12 mg/day compared to 5% for patients on placebo during forced weekly dose titration. While on a maintenance dose, the rates were 6% for patients on Exelon compared to 4% for those on placebo.

The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most Frequent Adverse Events Leading to Withdrawal from Clinical Trials during Titration and Maintenance in Patients Receiving 6-12 mg/day Exelon® Using a Forced Dose Titration

Study Phase	Titration		Maintenance		Overall	
	Placebo (n=868)	Exelon ≥6-12 mg/day (n=1189)	Placebo (n=788)	Exelon ≥6-12 mg/day (n=987)	Placebo (n=868)	Exelon ≥6-12 mg/day (n=1189)
Event/% Discontinuing						
Nausea	<1	8	<1	1	1	8
Vomiting	<1	4	<1	1	<1	5
Anorexia	0	2	<1	1	<1	3
Dizziness	<1	2	<1	1	<1	2

Most Frequent Adverse Clinical Events Seen in Association with the Use of Exelon

The most common adverse events, defined as those occurring at a frequency of at least 5% and twice the placebo rate, are largely predicted by Exelon's cholinergic effects. These include nausea, vomiting, anorexia, dyspepsia, and asthenia.

Gastrointestinal Adverse Reactions

Exelon use is associated with significant nausea, vomiting, and weight loss (see WARNINGS).

Adverse Events Reported in Controlled Trials

Table 2 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials and for which the rate of occurrence was greater for patients treated with Exelon doses of 6-12 mg/day than for those treated with placebo. The prescriber should be aware that these figures cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

In general, adverse reactions were less frequent later in the course of treatment.

No systematic effect of race or age could be determined on the incidence of adverse events in the controlled studies. Nausea, vomiting and weight loss were more frequent in women than men.

Table 2. Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Exelon® (6-12 mg/day) and at a Higher Frequency than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=868)	Exelon® (6-12 mg/day) (n=1189)
Percent of Patients with any Adverse Event	79	92
Autonomic Nervous System		
Sweating increased	1	4
Syncope	2	3
Body as a Whole		
Accidental Trauma	9	10
Fatigue	5	9
Asthenia	2	6
Malaise	2	5
Influenza-like Symptoms	2	3
Weight Decrease	<1	3
Cardiovascular Disorders, General		
Hypertension	2	3
Central and Peripheral Nervous System		
Dizziness	11	21
Headache	12	17
Somnolence	3	5
Tremor	1	4
Gastrointestinal System		
Nausea	12	47
Vomiting	6	31
Diarrhea	11	19
Anorexia	3	17
Abdominal Pain	6	13
Dyspepsia	4	9
Constipation	4	5
Flatulence	2	4
Eructation	1	2
Psychiatric Disorders		
Insomnia	7	9
Confusion	7	8
Depression	4	6
Anxiety	3	5
Hallucination	3	4
Aggressive Reaction	2	3
Resistance Mechanism Disorders		
Urinary Tract Infection	6	7
Respiratory System		
Rhinitis	3	4

Other adverse events observed at a rate of 2% or more on Exelon 6-12 mg/day but at a greater or equal rate on placebo were chest pain, peripheral edema, vertigo, back pain, arthralgia, pain, bone fracture, agitation, nervousness, delusion, paranoid reaction, upper respiratory tract infections, infection (general), coughing, pharyngitis, bronchitis, rash (general), urinary incontinence.

Other Adverse Events Observed During Clinical Trials

Exelon has been administered to over 5297 individuals during clinical trials worldwide. Of these, 4326 patients have been treated for at least 3 months, 3407 patients have been treated for at least 6 months, 2150 patients have been treated for 1 year, 1250 have been treated for 2 years, and 168 have been treated for over 3 years. With regard to exposure to the highest dose, 2809 patients were exposed to doses of 10-12 mg, 2615 patients treated for 3 months, 2328 patients treated for 6 months, 1378 patients treated for 1 year, 917 patients treated for 2 years, and 129 treated for over 3 years.

Treatment emergent signs and symptoms that occurred during 8 controlled clinical trials and 9 open-label trials in North America, Western Europe, Australia, South Africa, and Japan were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified WHO dictionary, and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 5297 patients from these trials who experienced that event while receiving Exelon. All adverse events occurring in at least 6 patients (approximately 0.1%) are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, relatively minor events, or events unlikely to be drug caused. Events are classified by body system and listed using the following definitions: frequent adverse events - those occurring in at least 1/100 patients; infrequent adverse events - those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to Exelon treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Autonomic Nervous System: *Infrequent:* Cold clammy skin, dry mouth, flushing, increased saliva.

Body as a Whole: *Frequent:* Accidental trauma, fever, edema, allergy, hot flushes, rigors. *Infrequent*: Edema periorbital or facial, hypothermia, edema, feeling cold, halitosis.

Cardiovascular System: *Frequent:* Hypotension, postural hypotension, cardiac failure.

Central and Peripheral Nervous System: *Frequent:* Abnormal gait, ataxia, paraesthesia, convulsions. *Infrequent:* Paresis, apraxia, aphasia, dysphonia, hyperkinesia, hyperreflexia, hypertonia, hypoesthesia, hypokinesia, migraine, neuralgia, nystagmus, peripheral neuropathy.

Endocrine System: *Infrequent:* Goitre, hypothyroidism.

Gastrointestinal System: *Frequent:* Fecal incontinence, gastritis. *Infrequent:* Dysphagia, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, GI hemorrhage, hernia, intestinal obstruction, melena, rectal hemorrhage, gastroenteritis, ulcerative stomatitis, duodenal ulcer, hematemesis, gingivitis, tenesmus, pancreatitis, colitis, glossitis.

Hearing and Vestibular Disorders: *Frequent:* Tinnitus.

Heart Rate and Rhythm Disorders: *Frequent:* Atrial fibrillation, bradycardia, palpitation. *Infrequent:* AV block, bundle branch block, sick sinus syndrome, cardiac arrest, supraventricular tachycardia, extrasystoles, tachycardia.

Liver and Biliary System Disorders: *Infrequent:* Abnormal hepatic function, cholecystitis.

Metabolic and Nutritional Disorders: *Frequent:* Dehydration, hypokalemia. *Infrequent:* Diabetes mellitus, gout, hypercholesterolemia, hyperlipernia, hypoglycemia, cachexia, thirst, hyperglycemia, hyponatremia.

Musculoskeletal Disorders: *Frequent:* Arthritis, leg cramps, myalgia. *Infrequent:* Cramps, hernia, muscle weakness.

Myo-, Endo-, Pericardial and Valve Disorders: *Frequent:* Angina pectoris, myocardial infarction.

Platelet, Bleeding, and Clotting Disorders: *Frequent:* Epistaxis. *Infrequent:* Hematoma, thrombocytopenia, purpura.

Psychiatric Disorders: *Frequent:* Paranoid reaction, confusion. *Infrequent:* Abnormal dreaming, amnesia, apathy, delirium, dementia, depersonalization, emotional lability, impaired concentration,

decreased libido, personality disorder, suicide attempt, increased libido, neurosis, suicidal ideation, psychosis.

Red Blood Cell Disorders: *Frequent:* Anemia. *Infrequent:* Hypochromic anemia.

Reproductive Disorders (Female & Male): *Infrequent:* Breast pain, impotence, atrophic vaginitis.

Resistance Mechanism Disorders: *Infrequent:* Cellulitis, cystitis, herpes simplex, otitis media.

Respiratory System: *Infrequent:* Bronchospasm, laryngitis, apnea.

Skin and Appendages: *Frequent:* Rashes of various kinds (maculopapular, eczema, bullous, exfoliative, psoriaform, erythematous). *Infrequent:* Alopecia, skin ulceration, urticaria, dermatitis contact.

Special Senses: *Infrequent:* Perversion of taste, loss of taste.

Urinary System Disorders: *Frequent:* Hematuria. *Infrequent:* Albuminuria, oliguria, acute renal failure, dysuria, micturition urgency, nocturia, polyuria, renal calculus, urinary retention.

Vascular (extracardiac) Disorders: *Infrequent:* Hemorrhoids, peripheral ischemia, pulmonary embolism, thrombosis, thrombophlebitis deep, aneurysm, hemorrhage intracranial.

Vision Disorders: *Frequent:* Cataract. *Infrequent:* Conjunctival hemorrhage, blepharitis, diplopia, eye pain, glaucoma.

White Cell and Resistance Disorders: *Infrequent:* Lymphadenopathy, leukocytosis.

Post-Introduction Reports

Voluntary reports of adverse events temporally associated with Exelon that have been received since market introduction that are not listed above, and that may or may not be causally related to the drug include the following:

Skin and Appendages: Stevens-Johnson syndrome

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.

As Exelon® (rivastigmine tartrate) has a short plasma half-life of about one hour and a moderate duration of acetylcholinesterase inhibition of 8-10 hours, it is recommended that in cases of asymptomatic overdoses, no further dose of Exelon should be administered for the next 24 hours.

As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Atypical responses in blood pressure and heart rate have been reported with other drugs that increase cholinergic activity when co-administered with quaternary anticholinergics such as glycopyrrolate. Due to the short half-life of Exelon, dialysis (hemodialysis, peritoneal dialysis, or hemofiltration) would not be clinically indicated in the event of an overdose.

In overdoses accompanied by severe nausea and vomiting, the use of antiemetics should be considered. In a documented case of a 46 mg overdose with Exelon, the patient experienced vomiting,

incontinence, hypertension, psychomotor retardation, and loss of consciousness. The patient fully recovered within 24 hours and conservative management was all that was required for treatment.

DOSAGE AND ADMINISTRATION

The dosage of Exelon® (rivastigmine tartrate) shown to be effective in controlled clinical trials is 6-12 mg/day, given as twice a day dosing (daily doses of 3 to 6 mg BID). There is evidence from the clinical trials that doses at the higher end of this range may be more beneficial.

The starting dose of Exelon is 1.5 mg twice a day (BID). If this dose is well tolerated, after a minimum of two weeks of treatment, the dose may be increased to 3 mg BID. Subsequent increases to 4.5 mg BID and 6 mg BID should be attempted after a minimum of 2 weeks at the previous dose. If adverse effects (e.g., nausea, vomiting, abdominal pain, loss of appetite) cause intolerance during treatment, the patient should be instructed to discontinue treatment for several doses and then restart at the same or next lower dose level. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose and titrated as described above (see Warnings). The maximum dose is 6 mg BID (12 mg/day).

Exelon should be taken with meals in divided doses in the morning and evening.

HOW SUPPLIED

Exelon® (rivastigmine tartrate) capsules equivalent to 1.5 mg, 3.0 mg, 4.5 mg, or 6.0 mg of rivastigmine base are available as follows:

1.5 mg Capsule – yellow, "Exelon 1,5 mg" is printed in red on the body of the capsule.

Bottles of 60 ..... NDC 0078-0323-44
Bottles of 500 ..... NDC 0078-0323-08
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 0078-0323-06

3.0 mg Capsule – orange, "Exelon 3 mg" is printed in red on the body of the capsule.

Bottles of 60 ..... NDC 0078-0324-44
Bottles of 500 ..... NDC 0078-0324-08
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 0078-0324-06

4.5 mg Capsule – red, "Exelon 4,5 mg" is printed in white on the body of the capsule.

Bottles of 60 ..... NDC 0078-0325-44
Bottles of 500 ..... NDC 0078-0325-08
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 0078-0325-06

6.0 mg Capsule - orange and red, "Exelon 6 mg" is printed in red on the body of the capsule.

Bottles of 60 ..... NDC 0078-0326-44
Bottles of 500 ..... NDC 0078-0326-08
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 0078-0326-06

Store below 77°F (25°C) in a tight container.

T2000-11
REV: DECEMBER 2000 Printed in U.S.A. 89007401

NOVARTIS

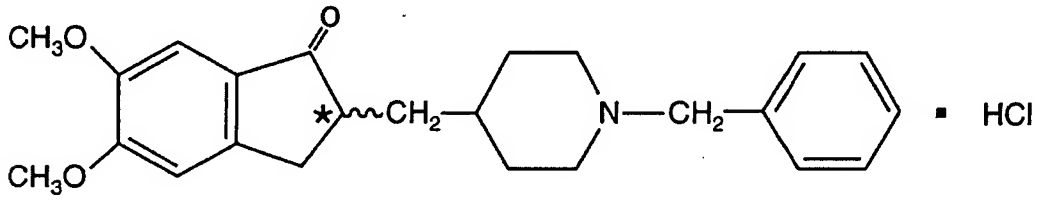
Manufactured by
Novartis Pharma AG
Basle, Switzerland

Manufactured for
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

ARICEPT®Oral Solution
(Donepezil Hydrochloride)

DESCRIPTION

ARICEPT® (donepezil hydrochloride) is a reversible inhibitor of the enzyme acetylcholinesterase, known chemically as (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1*H*-inden-1-one hydrochloride. Donepezil hydrochloride is commonly referred to in the pharmacological literature as E2020. It has an empirical formula of $C_{24}H_{29}NO_3HCl$ and a molecular weight of 415.96. Donepezil hydrochloride is a white crystalline powder and is freely soluble in chloroform, soluble in water and in glacial acetic acid, slightly soluble in ethanol and in acetonitrile and practically insoluble in ethyl acetate and in n-hexane.



Each 1mL of ARICEPT® Oral Solution contains 1 mg of donepezil hydrochloride. ARICEPT® Oral Solution also contains sorbitol solution 70%, povidone K-30, citric acid anhydrous, sodium citrate dihydrate, sodium benzoate, methylparaben, propylene glycol, sodium metabisulfite, purified water and strawberry flavor.

CLINICAL PHARMACOLOGY

Current theories on the pathogenesis of the cognitive signs and symptoms of Alzheimer's Disease attribute some of them to a deficiency of cholinergic neurotransmission.

Donepezil hydrochloride is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. If this proposed mechanism of action is correct, donepezil's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that donepezil alters the course of the underlying dementing process.

Clinical Trial Data

The effectiveness of ARICEPT® as a treatment for Alzheimer's Disease is demonstrated by the results of two randomized, double-blind, placebo-controlled clinical investigations

in patients with Alzheimer's Disease (diagnosed by NINCDS and DSM III-R criteria, Mini-Mental State Examination ≥ 10 and ≤ 26 and Clinical Dementia Rating of 1 or 2). The mean age of patients participating in ARICEPT® trials was 73 years with a range of 50 to 94. Approximately 62% of patients were women and 38% were men. The racial distribution was white 95%, black 3% and other races 2%.

Study Outcome Measures: In each study, the effectiveness of treatment with ARICEPT® was evaluated using a dual outcome assessment strategy.

The ability of ARICEPT® to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's Disease patients. The ADAS-cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis. The ADAS-cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment. Elderly normal adults may score as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher.

The patients recruited as participants in each study had mean scores on the Alzheimer's Disease Assessment Scale (ADAS-cog) of approximately 26 units, with a range from 4 to 61. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's Disease suggest that they gain 6 to 12 units a year on the ADAS-cog. However, lesser degrees of change are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in ARICEPT® trials was approximately 2 to 4 units per year.

The ability of ARICEPT® to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC plus. The CIBIC plus is not a single instrument and is not a standardized instrument like the ADAS-cog. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure.

As such, results from a CIBIC plus reflect clinical experience from the trial or trials in which it was used and cannot be compared directly with the results of CIBIC plus evaluations from other clinical trials. The CIBIC plus used in ARICEPT® trials was a semi-structured instrument that was intended to examine four major areas of patient function: General, Cognitive, Behavioral and Activities of Daily Living. It represents the assessment of a skilled clinician based upon his/her observations at an interview with the patient, in combination with information supplied by a caregiver familiar with the behavior of the patient over the interval rated. The CIBIC plus is scored as a seven point categorical rating, ranging from a score of 1, indicating "markedly improved," to a score of 4, indicating "no change" to a score of 7, indicating "markedly worse." The CIBIC plus has not been systematically compared directly to assessments not using information from caregivers (CIBIC) or other global methods.

Thirty-Week Study

In a study of 30 weeks duration, 473 patients were randomized to receive single daily doses of placebo, 5 mg/day or 10 mg/day of ARICEPT®. The 30-week study was divided into a 24-week double-blind active treatment phase followed by a 6-week single-blind placebo washout period. The study was designed to compare 5 mg/day or 10 mg/day fixed doses of ARICEPT® to placebo. However, to reduce the likelihood of cholinergic effects, the 10 mg/day treatment was started following an initial 7-day treatment with 5 mg/day doses.

Effects on the ADAS-cog: Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 30 weeks of the study. After 24 weeks of treatment, the mean differences in the ADAS-cog change scores for ARICEPT® treated patients compared to the patients on placebo were 2.8 and 3.1 units for the 5 mg/day and 10 mg/day treatments, respectively. These differences were statistically significant. While the treatment effect size may appear to be slightly greater for the 10 mg/day treatment, there was no statistically significant difference between the two active treatments.

Following 6 weeks of placebo washout, scores on the ADAS-cog for both the ARICEPT® treatment groups were indistinguishable from those patients who had received only placebo for 30 weeks. This suggests that the beneficial effects of ARICEPT® abate over 6 weeks following discontinuation of treatment and do not represent a change in the underlying disease. There was no evidence of a rebound effect 6 weeks after abrupt discontinuation of therapy.

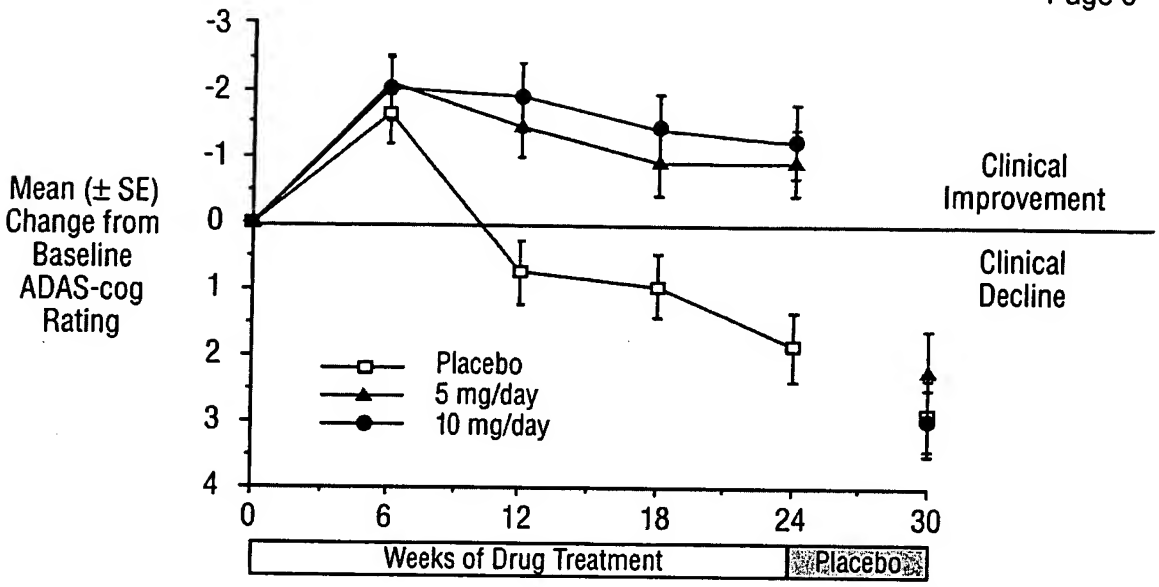


Figure 1. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks of Treatment.

Figure 2 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained the measure of improvement in ADAS-cog score shown on the X axis. Three change scores, (7-point and 4-point reductions from baseline or no change in score) have been identified for illustrative purposes and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to placebo and ARICEPT® have a wide range of responses, but that the active treatment groups are more likely to show the greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon or shifted to the right of the curve for placebo, respectively.

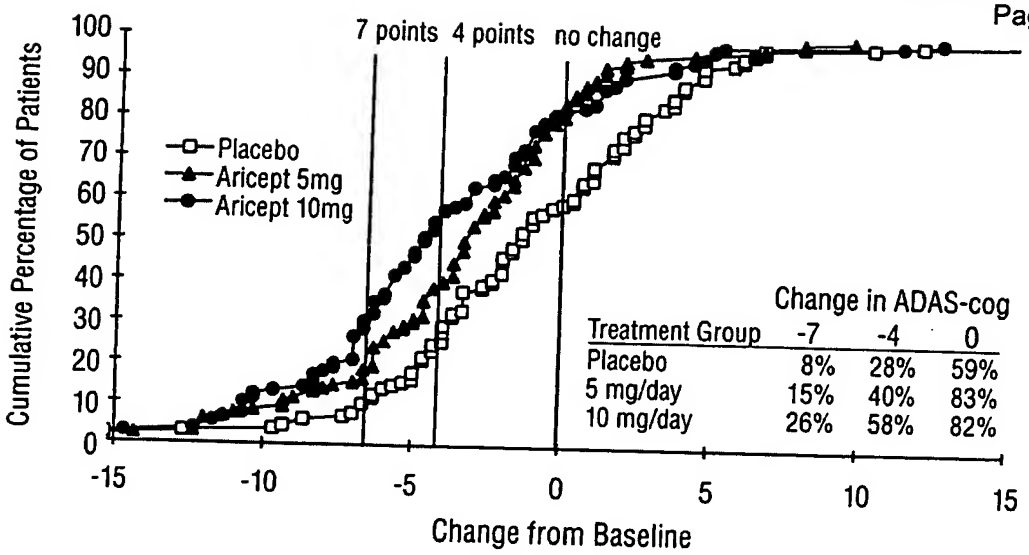


Figure 2. Cumulative Percentage of Patients Completing 24 Weeks of Double-blind Treatment with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 80%, 5 mg/day 85% and 10 mg/day 68%.

Effects on the CIBIC plus: Figure 3 is a histogram of the frequency distribution of CIBIC plus scores attained by patients assigned to each of the three treatment groups who completed 24 weeks of treatment. The mean drug-placebo differences for these groups of patients were 0.35 units and 0.39 units for 5 mg/day and 10 mg/day of ARICEPT®, respectively. These differences were statistically significant. There was no statistically significant difference between the two active treatments.

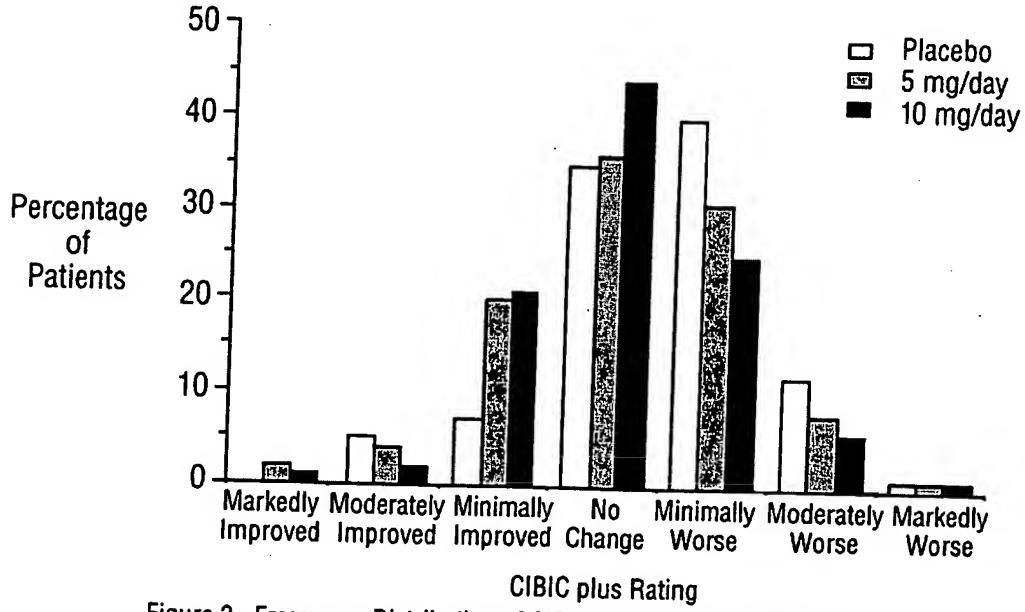


Figure 3. Frequency Distribution of CIBIC plus Scores at Week 24

Fifteen-Week Study

In a study of 15 weeks duration, patients were randomized to receive single daily doses of placebo or either 5 mg/day or 10 mg/day of ARICEPT® for 12 weeks, followed by a 3-week placebo washout period. As in the 30-week study, to avoid acute cholinergic effects, the 10 mg/day treatment followed an initial 7-day treatment with 5 mg/day doses.

Effects on the ADAS-Cog: Figure 4 illustrates the time course of the change from baseline in ADAS-cog scores for all three dose groups over the 15 weeks of the study. After 12 weeks of treatment, the differences in mean ADAS-cog change scores for the ARICEPT® treated patients compared to the patients on placebo were 2.7 and 3.0 units each, for the 5 and 10 mg/day ARICEPT®treatment groups respectively. These differences were statistically significant. The effect size for the 10 mg/day group may appear to be slightly larger than that for 5 mg/day. However, the differences between active treatments were not statistically significant.

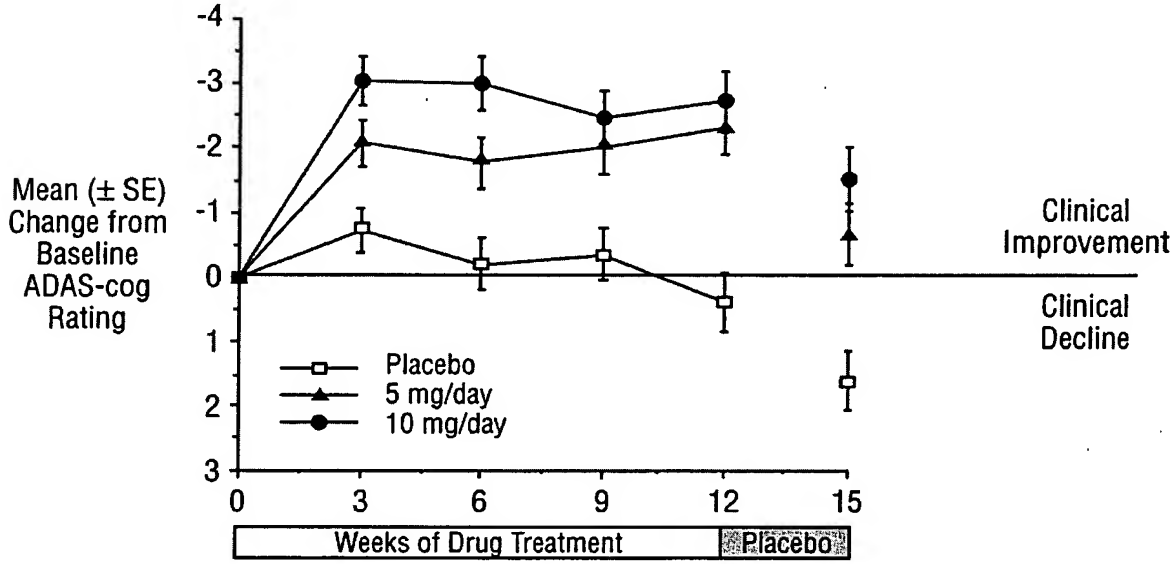


Figure 4. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing the 15-week Study.

Following 3 weeks of placebo washout, scores on the ADAS-cog for both the ARICEPT® treatment groups increased, indicating that discontinuation of ARICEPT® resulted in a loss of its treatment effect. The duration of this placebo washout period was not sufficient to characterize the rate of loss of the treatment effect, but, the 30-week study (see above) demonstrated that treatment effects associated with the use of ARICEPT® abate within 6 weeks of treatment discontinuation.

Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who attained the measure of improvement in ADAS-cog score shown

on the X axis. The same three change scores, (7-point and 4-point reductions from baseline or no change in score) as selected for the 30-week study have been used for this illustration. The percentages of patients achieving those results are shown in the inset table.

As observed in the 30-week study, the curves demonstrate that patients assigned to either placebo or to ARICEPT® have a wide range of responses, but that the ARICEPT® treated patients are more likely to show the greater improvements in cognitive performance.

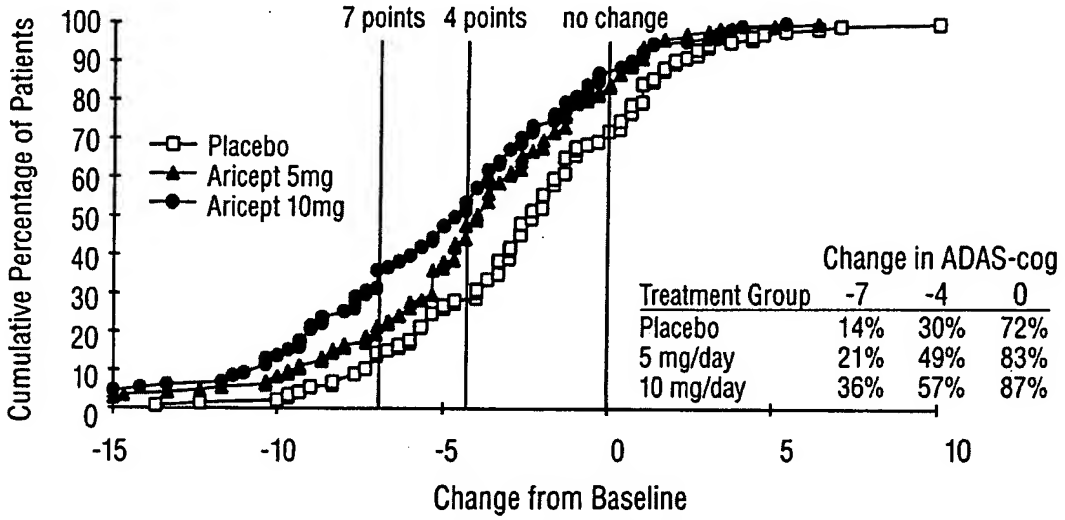


Figure 5. Cumulative Percentage of Patients with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients Within Each Treatment Group Who Completed the Study Were: Placebo 93%, 5 mg/day 90% and 10 mg/day 82%.

Effects on the CIBIC plus: Figure 6 is a histogram of the frequency distribution of CIBIC plus scores attained by patients assigned to each of the three treatment groups who completed 12 weeks of treatment. The differences in mean scores for ARICEPT® treated patients compared to the patients on placebo at Week 12 were 0.36 and 0.38 units for the 5 mg/day and 10 mg/day treatment groups, respectively. These differences were statistically significant.

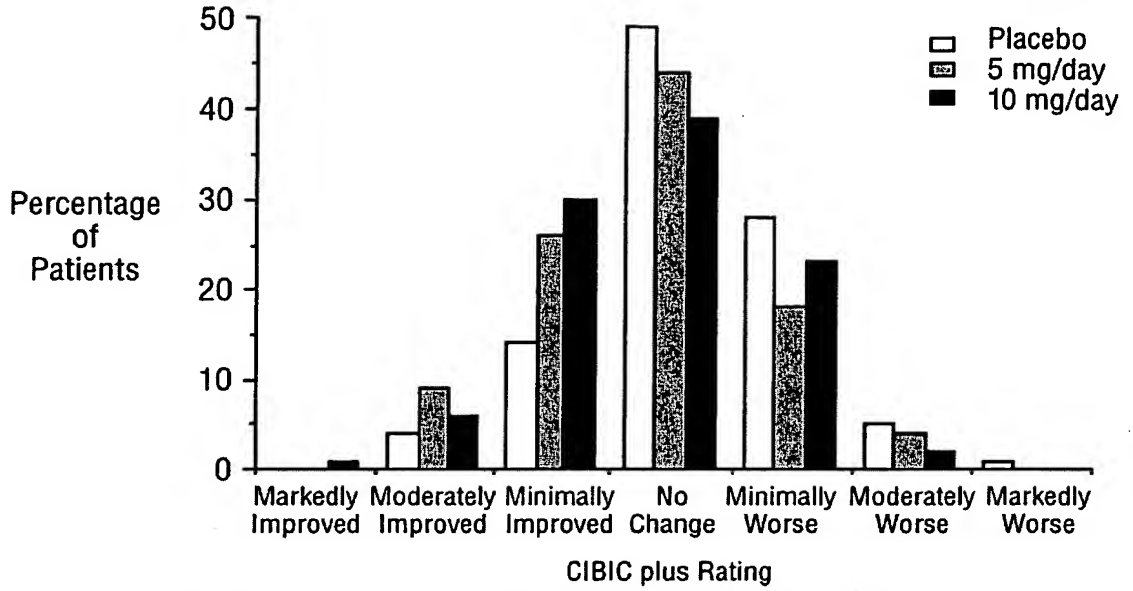


Figure 6. Frequency Distribution of CIBIC plus Scores at Week 12

In both studies, patient age, sex and race were not found to predict the clinical outcome of ARICEPT® treatment.

Clinical Pharmacokinetics

ARICEPT® Oral Solution is bioequivalent to ARICEPT® Tablets. Donepezil is well absorbed with a relative oral bioavailability of 100% and reaches peak plasma concentrations in 3 to 4 hours. Pharmacokinetics are linear over a dose range of 1-10 mg given once daily. Neither food nor time of administration (morning vs. evening dose) influences the rate or extent of absorption of ARICEPT® tablets. Administration of ARICEPT® Oral Solution to healthy volunteers with a high-fat meal decreased C_{max} by 17% and increased T_{max} by 1 hour, while the AUC_{0-72} was similar under fed and fasted conditions. This delay in absorption and decrease in exposure is not likely to be clinically significant; therefore, ARICEPT® Oral Solution can be taken without regard to meals.

The elimination half life of donepezil is about 70 hours and the mean apparent plasma clearance (Cl/F) is 0.13 L/hr/kg. Following multiple dose administration, donepezil accumulates in plasma by 4-7 fold and steady state is reached within 15 days. The steady state volume of distribution is 12 L/kg. Donepezil is approximately 96% bound to human plasma proteins, mainly to albumins (about 75%) and $alpha_1$ - acid glycoprotein (about 21%) over the concentration range of 2-1000 ng/mL.

Donepezil is both excreted in the urine intact and extensively metabolized to four major metabolites, two of which are known to be active, and a number of minor metabolites, not all of which have been identified. Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. Following administration of ^{14}C-labeled

donepezil, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil (53%) and as 6-O-desmethyl donepezil (11%), which has been reported to inhibit AChE to the same extent as donepezil *in vitro* and was found in plasma at concentrations equal to about 20% of donepezil. Approximately 57% and 15% of the total radioactivity was recovered in urine and feces, respectively, over a period of 10 days, while 28% remained unrecovered, with about 17% of the donepezil dose recovered in the urine as unchanged drug.

Special Populations:

Hepatic Disease: In a study of 10 patients with stable alcoholic cirrhosis, the clearance of ARICEPT® was decreased by 20% relative to 10 healthy age and sex matched subjects.

Renal Disease: In a study of 11 patients with moderate to severe renal impairment (Cl_{Cr} < 18 mL/min/1.73 m^2) the clearance of ARICEPT® did not differ from 11 age and sex matched healthy subjects.

Age: No formal pharmacokinetic study was conducted to examine age related differences in the pharmacokinetics of ARICEPT®. However, mean plasma ARICEPT® concentrations measured during therapeutic drug monitoring of elderly patients with Alzheimer's Disease are comparable to those observed in young healthy volunteers.

Gender and Race: No specific pharmacokinetic study was conducted to investigate the effects of gender and race on the disposition of ARICEPT®. However, retrospective pharmacokinetic analysis indicates that gender and race (Japanese and Caucasians) did not affect the clearance of ARICEPT®.

Drug-Drug Interactions

Drugs Highly Bound to Plasma Proteins: Drug displacement studies have been performed *in vitro* between this highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. ARICEPT® at concentrations of 0.3-10 μg/mL did not affect the binding of furosemide (5 μg/mL), digoxin (2 ng/mL), and warfarin (3 μg/mL) to human albumin. Similarly, the binding of ARICEPT® to human albumin was not affected by furosemide, digoxin and warfarin.

Effect of ARICEPT® on the Metabolism of Other Drugs: No *in vivo* clinical trials have investigated the effect of ARICEPT® on the clearance of drugs metabolized by CYP 3A4 (e.g. cisapride, terfenadine) or by CYP 2D6 (e.g. imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean K_i about 50-130 μM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference.

Whether ARICEPT® has any potential for enzyme induction is not known.

Formal pharmacokinetic studies evaluated the potential of ARICEPT® for interaction with theophylline, cimetidine, warfarin, digoxin and ketoconazole. No effects of ARICEPT® on the pharmacokinetics of these drugs were observed.

Effect of Other Drugs on the Metabolism of ARICEPT® : Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Whether there is a clinical effect of quinidine is not known. In a 7-day crossover study in 18 healthy volunteers, ketoconazole (200mg q.d.) increased mean donepezil (5mg q.d.) concentrations (AUC_{0-24} and C_{max}) by 36%. The clinical relevance of this increase in concentration is unknown.

Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of ARICEPT®.

Formal pharmacokinetic studies demonstrated that the metabolism of ARICEPT® is not significantly affected by concurrent administration of digoxin or cimetidine.

INDICATIONS AND USAGE

ARICEPT® is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRAINDICATIONS

ARICEPT® is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives.

WARNINGS

Anesthesia: ARICEPT®, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Cardiovascular Conditions: Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of ARICEPT®.

Gastrointestinal Conditions: Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of ARICEPT® have shown no increase,

relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

ARICEPT®, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT®.

Genitourinary: Although not observed in clinical trials of ARICEPT®, cholinomimetics may cause bladder outflow obstruction.

Neurological Conditions: Seizures: Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's Disease.

Pulmonary Conditions: Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

Sulfites:

ARICEPT® Oral Solution contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than nonasthmatic people.

PRECAUTIONS

Drug-Drug Interactions (see Clinical Pharmacology: Clinical Pharmacokinetics: Drug-drug Interactions)

Effect of ARICEPT® on the Metabolism of Other Drugs: No *in vivo* clinical trials have investigated the effect of ARICEPT® on the clearance of drugs metabolized by CYP 3A4 (e.g. cisapride, terfenadine) or by CYP 2D6 (e.g. imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean K_i about 50-130 μM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference.

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Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of ARICEPT®.

Formal pharmacokinetic studies demonstrated that the metabolism of ARICEPT® is not significantly affected by concurrent administration of digoxin or cimetidine.

Use with Anticholinergics: Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

Use with Cholinomimetics and Other Cholinesterase Inhibitors: A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a carcinogenic potential was obtained in an 88-week carcinogenicity study of donepezil hydrochloride conducted in CD-1 mice at doses up to 180 mg/kg/day (approximately 90 times the maximum recommended human dose on a mg/m^2 basis), or in a 104-week carcinogenicity study in Sprague-Dawley rats at doses up to 30mg/kg/day (approximately 30 times the maximum recommended human dose on a mg/m^2 basis).

Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria, or in a mouse lymphoma forward mutation assay *in vitro*. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed. Donepezil was not clastogenic in the *in vivo* mouse micronucleus test and was not genotoxic in an *in vivo* unscheduled DNA synthesis assay in rats.

Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m^2 basis).

Pregnancy

Pregnancy Category C: Teratology studies conducted in pregnant rats at doses up to 16 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/m^2 basis) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m^2 basis) did not disclose any evidence for a teratogenic potential of donepezil. However, in a study in which pregnant

rats were given up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m^2 basis) from day 17 of gestation through day 20 postpartum, there was a slight increase in still births and a slight decrease in pup survival through day 4 postpartum at this dose; the next lower dose tested was 3 mg/kg/day. There are no adequate or well-controlled studies in pregnant women. ARICEPT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether donepezil is excreted in human breast milk. ARICEPT® has no indication for use in nursing mothers.

Pediatric Use

There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT® in any illness occurring in children.

Geriatric Use

Alzheimer's disease is a disorder occurring primarily in individuals over 55 years of age. The mean age of patients enrolled in the clinical studies with ARICEPT® was 73 years; 80% of these patients were between 65 and 84 years old and 49% of patients were at or above the age of 75. The efficacy and safety data presented in the clinical trials section were obtained from these patients. There were no clinically significant differences in most adverse events reported by patient groups ≥ 65 years old and < 65 years old.

ADVERSE REACTIONS

Adverse Events Leading to Discontinuation

The rates of discontinuation from controlled clinical trials of ARICEPT® due to adverse events for the ARICEPT® 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received 7-day escalations from 5 mg/day to 10 mg/day, was higher at 13%.

The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most Frequent Adverse Events Leading to Withdrawal from Controlled Clinical Trials by Dose Group

Dose Group	Placebo	5 mg/day ARICEPT®	10 mg/day ARICEPT®
Patients Randomized	355	350	315
Event/%Discontinuing			
Nausea	1%	1%	3%
Diarrhea	0%	<1%	3%
Vomiting	<1%	<1%	2%

Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT®

The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by ARICEPT®'s cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT® treatment without the need for dose modification.

There is evidence to suggest that the frequency of these common adverse events may be affected by the rate of titration. An open-label study was conducted with 269 patients who received placebo in the 15 and 30-week studies. These patients were titrated to a dose of 10 mg/day over a 6-week period. The rates of common adverse events were lower than those seen in patients titrated to 10 mg/day over one week in the controlled clinical trials and were comparable to those seen in patients on 5 mg/day.

See Table 2 for a comparison of the most common adverse events following one and six week titration regimens.

Table 2. Comparison of rates of adverse events in patients titrated to 10 mg/day over 1 and 6 weeks

	No titration		One week titration	Six week titration
Adverse Event	**Placebo (n=315)**	**5 mg/day (n=311)**	**10 mg/day (n=315)**	**10 mg/day (n=269)**
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle cramps	2%	6%	8%	3%
Anorexia	2%	3%	7%	3%

Adverse Events Reported in Controlled Trials

The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 3 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received ARICEPT® and for which the rate of occurrence was greater for ARICEPT® assigned than placebo assigned patients. In general, adverse events occurred more frequently in female patients and with advancing age.

Table 3. Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving ARICEPT® and at a Higher Frequency than Placebo-treated Patients		
Body System/Adverse Event	**Placebo (n=355)**	**ARICEPT® (n=747)**
Percent of Patients with any Adverse Event	**72**	**74**
Body as a Whole		
Headache	9	10
Pain, various locations	8	9
Accident	6	7
Fatigue	3	5
Cardiovascular System		
Syncope	1	2
Digestive System		
Nausea	6	11
Diarrhea	5	10
Vomiting	3	5
Anorexia	2	4
Hemic and Lymphatic System		
Ecchymosis	3	4
Metabolic and Nutritional Systems		
Weight Decrease	1	3
Musculoskeletal System		
Muscle Cramps	2	6
Arthritis	1	2
Nervous System		
Insomnia	6	9
Dizziness	6	8
Depression	<1	3
Abnormal Dreams	0	3
Somnolence	<1	2
Urogenital System		
Frequent Urination	1	2

Other Adverse Events Observed During Clinical Trials

ARICEPT® has been administered to over 1700 individuals during clinical trials worldwide. Approximately 1200 of these patients have been treated for at least 3 months and more than 1000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 116 patients treated for over 1 year. The range of patient exposure is from 1 to 1214 days.

Treatment emergent signs and symptoms that occurred during 3 controlled clinical trials and two open-label trials in the United States were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were

grouped into a smaller number of standardized categories using a modified COSTART dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving ARICEPT®. All adverse events occurring at least twice are included, except for those already listed in Tables 2 or 3, COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed using the following definitions: *frequent adverse events* - those occurring in at least 1/100 patients; *infrequent adverse events* - those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to ARICEPT® treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. No important additional adverse events were seen in studies conducted outside the United States.

Body as a Whole: *Frequent:* influenza, chest pain, toothache; *Infrequent:* fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, listlessness.

Cardiovascular System: *Frequent:* hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; *Infrequent:* angina pectoris, postural hypotension, myocardial infarction, AV block (first degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thrombosis.

Digestive System: *Frequent:* fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; *Infrequent:* eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, hemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer.

Endocrine System: *Infrequent:* diabetes mellitus, goiter.

Hemic and Lymphatic System: *Infrequent:* anemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia.

Metabolic and Nutritional Disorders: *Frequent:* dehydration; *Infrequent:* gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase.

Musculoskeletal System: *Frequent:* bone fracture; *Infrequent:* muscle weakness, muscle fasciculation.

Nervous System: *Frequent:* delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, nervousness, aphasia; *Infrequent:* cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia,

dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing.

Respiratory System: *Frequent:* dyspnea, sore throat, bronchitis; *Infrequent:* epistaxis, post nasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring.

Skin and Appendages: *Frequent:* pruritus, diaphoresis, urticaria; *Infrequent:* dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer.

Special Senses: *Frequent:* cataract, eye irritation, vision blurred; *Infrequent:* dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes.

Urogenital System: *Frequent:* urinary incontinence, nocturia; *Infrequent:* dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis.

Postintroduction Reports

Voluntary reports of adverse events temporally associated with ARICEPT® that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, neuroleptic malignant syndrome, pancreatitis, and rash.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.

As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT® overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether

ARICEPT® and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).

Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation and lower body surface temperature.

DOSAGE AND ADMINISTRATION

The dosages of ARICEPT® shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once per day.

The higher dose of 10 mg did not provide a statistically significantly greater clinical benefit than 5 mg. There is a suggestion, however, based upon order of group mean scores and dose trend analyses of data from these clinical trials, that a daily dose of 10 mg of ARICEPT® might provide additional benefit for some patients. Accordingly, whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference.

Evidence from the controlled trials indicates that the 10 mg dose, with a one week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5 mg dose. In open label trials using a 6 week titration, the frequency of these same adverse events was similar between the 5 mg and 10 mg dose groups. Therefore, because steady state is not achieved for 15 days and because the incidence of untoward effects may be influenced by the rate of dose escalation, treatment with a dose of 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4 to 6 weeks.

Each teaspoon (5 mL) of ARICEPT® Oral Solution contains a 5 mg dose. Patients should be instructed as to how to measure their dose of ARICEPT® Oral Solution in teaspoons.

ARICEPT® Oral Solution should be taken in the evening, just prior to retiring. ARICEPT® Oral Solution can be taken with or without food.

HOW SUPPLIED

ARICEPT® Oral Solution is a clear, colorless to light yellow solution containing 1 mg of donepezil hydrochloride in each mL (1 mg/mL). Each teaspoon (5mL) contains 5 mg of donepezil hydrochloride.

NDC#62856-851-30 300 mL HDPE Bottles

R_x only

ARICEPT® is a registered trademark of
Eisai Co., Ltd.
Manufactured and Marketed by Eisai Inc., Teaneck, NJ 07666
Marketed by
Pfizer Inc, New York, NY 10017

STALEVO™ LABELING

STALEVO™ 50
STALEVO™ 100
STALEVO™ 150
(carbidopa, levodopa and entacapone) Tablets

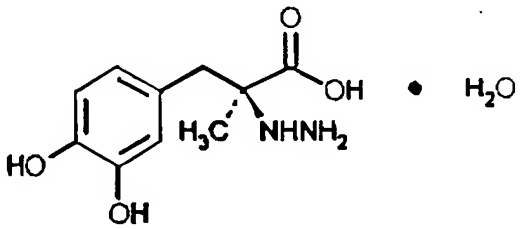
Rx only

Prescribing Information

DESCRIPTION

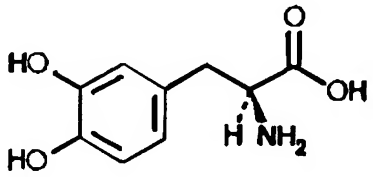
STALEVO™ (carbidopa, levodopa and entacapone) is a combination of carbidopa, levodopa and entacapone for the treatment of Parkinson's disease.

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (-)-L-(α-hydrazino-(α-methyl-β-(3,4-dihydroxybenzene) propanoic acid monohydrate. Its empirical formula is $C_{10}H_{14}N_2O_4 \cdot H_2O$, and its structural formula is

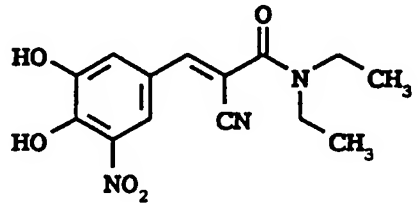


Tablet content is expressed in terms of anhydrous carbidopa, which has a molecular weight of 226.3.

Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (-)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid. Its empirical formula is $C_9H_{11}NO_4$, and its structural formula is



Entacapone, an inhibitor of catechol-*O*-methyltransferase (COMT), is a nitro-catechol-structured compound with a molecular weight of 305.3. The chemical name of entacapone is (E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide. Its empirical formula is $C_{14}H_{15}N_3O_5$ and its structural formula is



STALEVO™ (carbidopa, levodopa and entacapone) is supplied as tablets in three strengths:

STALEVO 50, containing 12.5mg of carbidopa, 50mg of levodopa and 200mg of entacapone

STALEVO 100, containing 25mg of carbidopa, 100mg of levodopa and 200mg of entacapone

STALEVO 150, containing 37.5mg of carbidopa, 150mg of levodopa and 200mg of entacapone

The inactive ingredients of the STALEVO tablet are corn starch, croscarmellose sodium, glycerol 85%, hypromellose, magnesium stearate, mannitol, polysorbate 80, povidone, sucrose, red iron oxide, titanium dioxide, and yellow iron oxide.

CLINICAL PHARMACOLOGY

Parkinson's disease is a progressive, neurodegenerative disorder of the extrapyramidal nervous system affecting the mobility and control of the skeletal muscular system. Its characteristic features include resting tremor, rigidity, and bradykinetic movements.

Mechanism of Action

Levodopa

Current evidence indicates that symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease apparently because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves symptoms of Parkinson's disease.

Carbidopa

When levodopa is administered orally it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to

the central nervous system. Carbidopa inhibits the decarboxylation of peripheral levodopa, making more levodopa available for transport to the brain. When coadministered with levodopa, carbidopa increases plasma levels of levodopa and reduces the amount of levodopa required to produce a given response by about 75 %. Carbidopa prolongs the plasma half-life of levodopa from 50 minutes to 1.5 hours and decreases plasma and urinary dopamine and its major metabolite, homovanillic acid. The t_{max} of levodopa, however, was unaffected by the coadministration.

Entacapone

Entacapone is a selective and reversible inhibitor of catechol-O-methyltransferase (COMT).

In mammals, COMT is distributed throughout various organs with the highest activities in the liver and kidney. COMT also occurs in neuronal tissues, especially in glial cells. COMT catalyzes the transfer of the methyl group of S-adenosyl-L-methionine to the phenolic group of substrates that contain a catechol structure. Physiological substrates of COMT include DOPA, catecholamines (dopamine, norepinephrine, and epinephrine) and their hydroxylated metabolites. The function of COMT is the elimination of biologically active catechols and some other hydroxylated metabolites. When decarboxylation of levodopa is prevented by carbidopa, COMT becomes the major metabolizing enzyme for levodopa, catalyzing its metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD).

When entacapone is given in conjunction with levodopa and carbidopa, plasma levels of levodopa are greater and more sustained than after administration of levodopa and carbidopa alone. It is believed that at a given frequency of levodopa administration, these more sustained plasma levels of levodopa result in more constant dopaminergic stimulation in the brain, leading to greater effects on the signs and symptoms of Parkinson's disease. The higher levodopa levels may also lead to increased levodopa adverse effects, sometimes requiring a decrease in the dose of levodopa.

When 200 mg entacapone is coadministered with levodopa/carbidopa, it increases levodopa plasma exposure (AUC) by 35-40% and prolongs its elimination half-life in Parkinson's disease patients from 1.3 to 2.4 hours. Plasma levels of the major COMT-mediated dopamine metabolite, 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD), are also markedly decreased proportionally with increasing dose of entacapone.

In animals, while entacapone enters the CNS to a minimal extent, it has been shown to inhibit central COMT activity. In humans, entacapone inhibits the COMT enzyme in peripheral tissues. The effects of entacapone on central COMT activity in humans have not been studied.

Pharmacokinetics

The pharmacokinetics of Stalevo tablets have been studied in healthy subjects (age 45-75 years old). Overall, following administration of corresponding doses of levodopa, carbidopa and

entacapone as STALEVO or as carbidopa/levodopa product plus Comtan® (entacapone) tablets, the mean plasma concentrations of levodopa, carbidopa, and entacapone are comparable.

Absorption/Distribution:
Both levodopa and entacapone are rapidly absorbed and eliminated, and their distribution volume is moderately small. Carbidopa is absorbed and eliminated slightly more slowly compared with levodopa and entacapone. There are substantial inter- and intra-individual variations in the absorption of levodopa, carbidopa and entacapone, particularly concerning its C_{max}

The food-effect on the STALEVO tablet has not been evaluated.

Levodopa

The pharmacokinetic properties of levodopa following the administration of single dose STALEVO™ (carbidopa, levodopa and entacapone) tablets are summarized in Table 1.

Table 1. Pharmacokinetic characteristics of levodopa with different tablet strengths of STALEVO (mean ±SD)

Tablet strength	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)
12.5 - 50 - 200 mg	1040 ± 314	470 ± 154	1.1 ± 0.5
25 - 100 - 200 mg	2910 ± 715	975 ± 247	1.4 ± 0.6
37.5 - 150 - 200 mg	3770 ± 1120	1270 ± 329	1.5 ± 0.9

Since levodopa competes with certain amino acids for transport across the gut wall, the absorption of levodopa may be impaired in some patients on a high protein diet. Meals rich in large neutral amino acids may delay and reduce the absorption of levodopa (see PRECAUTIONS).

Levodopa is bound to plasma protein only to a minor extent (about 10-30%).

Carbidopa

Following administration of STALEVO as a single dose to healthy male and female subjects, the peak concentration of carbidopa was reached within 2.5 to 3.4 hours on average. The mean C_{max} ranged from about 40 to 125 ng/ml and the mean AUC from 170 to 700 ng·h/mL, with different STALEVO strengths providing 12.5 mg, 25 mg, or 37.5 mg of carbidopa.

Carbidopa is approximately 36 % bound to plasma protein.

Entacapone

Following administration of STALEVO as a single dose to healthy male and female subjects, the peak concentration of entacapone in plasma was reached within 1.0 to 1.2 hours on average. The mean C_{max} of entacapone was about 1200 ng/mL and the AUC 1250 to 1450 ng•h/mL after administration of different STALEVO strengths all providing 200 mg of entacapone.

The plasma protein binding of entacapone is 98% over the concentration range of 0.4 - 50 µg/mL. Entacapone binds mainly to serum albumin.

Metabolism and Elimination:

Levodopa
The elimination half-life of levodopa, the active moiety of antiparkinsonian activity, was 1.7 hours (range 1.1-3.2 hours).

Levodopa is extensively metabolized to various metabolites. Two major pathways are decarboxylation by dopa decarboxylase (DDC) and O-methylation by catechol-O-methyltransferase (COMT).

Carbidopa
The elimination half-life of carbidopa was on average 1.6 to 2 hours (range 0.7-4.0 hours).

Carbidopa is metabolized to two main metabolites (á-methyl-3-methoxy-4-hydroxyphenylpropionic acid and á-methyl-3,4-dihydroxyphenylpropionic acid). These 2 metabolites are primarily eliminated in the urine unchanged or as glucuronide conjugates. Unchanged carbidopa accounts for 30% of the total urinary excretion.

Entacapone
The elimination half-life of entacapone was on average 0.8 to 1 hours (0.3-4.5 hours).

Entacapone is almost completely metabolized prior to excretion with only a very small amount (0.2% of dose) found unchanged in urine. The main metabolic pathway is isomerization to the cis-isomer, the only active metabolite. Entacapone and the cis-isomer are eliminated in the urine as glucuronide conjugates. The glucuronides account for 95 % of all urinary metabolites (70% as parent- & 25% as cis-isomer- glucuronides). The glucuronide conjugate of the cis-isomer is inactive. After oral administration of a 14C-labeled dose of entacapone, 10% of labeled parent and metabolite is excreted in urine and 90% in feces.

Due to short elimination half-lives, no true accumulation of levodopa or entacapone occurs when they are administered repeatedly.

Special Populations:

Hepatic Impairment:

STALEVO™ (carbidopa, levodopa and entacapone)

While there are no studies on the pharmacokinetics of carbidopa and levodopa in patients with hepatic impairment, STALEVO should be administered cautiously to patients with biliary obstruction or hepatic disease since biliary excretion appears to be the major route of excretion of entacapone and hepatic impairment had a significant effect on the pharmacokinetics of entacapone when 200mg entacapone was administered alone.

Entacapone

Hepatic impairment had a significant effect on the pharmacokinetics of entacapone when 200mg entacapone was administered alone. A single 200mg dose of entacapone, without levodopa/dopa decarboxylase inhibitor coadministration, showed approximately twofold higher AUC and C_{max} values in patients with a history of alcoholism and hepatic impairment (n=10) compared to normal subjects (n=10). All patients had biopsy-proven liver cirrhosis caused by alcohol. According to Child-Pugh grading 7 patients with liver disease had mild hepatic impairment and 3 patients had moderate hepatic impairment. As only about 10% of the entacapone dose is excreted in urine, as parent compound and conjugated glucuronide, biliary excretion appears to be the major route of excretion of this drug. Consequently, STALEVO should be administered with care to patients with biliary obstruction or hepatic disease.

Renal Impairment:

STALEVO™ (carbidopa, levodopa and entacapone):

STALEVO should be administered cautiously to patients with severe renal disease. There are no studies on the pharmacokinetics of levodopa and carbidopa in patients with renal impairment.

Entacapone:

No important effects of renal function on the pharmacokinetics of entacapone were found. The pharmacokinetics of entacapone have been investigated after a single 200-mg entacapone dose, without levodopa-dopa decarboxylase inhibitor coadministration, in a specific renal impairment study. There were three groups: normal subjects (n=7; creatinine clearance >1.12 mL/sec/1.73 m^2), moderate impairment (n=10; creatinine clearance ranging from 0.60 - 0.89 mL/sec/1.73 m^2), and severe impairment (n=7; creatinine clearance ranging from 0.20 - 0.44 mL/sec/1.73 m^2).

Concurrent Diseases

STALEVO should be administered cautiously to patients with biliary obstruction, hepatic disease, severe cardiovascular or pulmonary disease, bronchial asthma, renal, or endocrine disease.

Elderly:
STALEVO tablets have not been studied in Parkinson's disease patients or in healthy volunteers older than 75 years old. In the pharmacokinetics studies conducted in healthy volunteers following single dose of carbidopa/levodopa/entacapone (as STALEVO or as separate carbidopa/levodopa and Comtan tablets):

Levodopa

The AUC of levodopa is significantly (on average 10 - 20%) higher in elderly (60-75 years) than younger subjects (45-60 years). There is no significant difference in the C_{max} of levodopa between younger (45–60 years) and elderly subjects (60–75 years).

Carbidopa

There is no significant difference in the C_{max} and AUC of carbidopa, between younger (45 – 60 years) and elderly subjects (60–75 years).

Entacapone

The AUC of entacapone is significantly (on average, 15%) higher in elderly (60-75 years) than younger subjects (45-60 years). There is no significant difference in the C_{max} of entacapone between younger (45–60 years) and elderly subjects (60–75 years).

Gender:
The bioavailability of levodopa is significantly higher in females when given with or without carbidopa and/or entacapone. Following a single dose of carbidopa, levodopa and entacapone together, either as STALEVO or as separate carbidopa/levodopa and Comtan tablets in healthy volunteers (age range 45-74 years):

Levodopa
The plasma exposure (AUC & C_{max}) of levodopa is significantly higher in females than males (on average, 40% for AUC and 30% for C_{max}). These differences are primarily explained by body weight. Other published literature showed significant gender effect (higher concentrations in females) even after correction for body weight.

Carbidopa:
There is no gender difference in the pharmacokinetics of carbidopa.

Entacapone:
There is no gender difference in the pharmacokinetics of entacapone.

Drug Interactions: See PRECAUTIONS, Drug Interactions

Clinical Studies

Each STALEVO™ (carbidopa, levodopa and entacapone) tablet, provided in three single-dose strengths, contains carbidopa and levodopa in ratio 1:4 and a 200mg dose of entacapone. The three STALEVO tablet strengths have been shown to be bioequivalent to the corresponding doses of standard release carbidopa-levodopa 25-100mg tablets and Comtan 200mg tablets.

The effectiveness of entacapone as an adjunct to levodopa in the treatment of Parkinson's disease was established in three 24-week multicenter, randomized, double blind placebo-controlled trials in patients with Parkinson's disease. In two of these trials, the patients' disease was "fluctuating", i.e., was characterized by documented periods of "On" (periods of relatively good functioning) and "Off" (periods of relatively poor functioning), despite optimum levodopa therapy. There was also a withdrawal period following 6 months of treatment. In the third trial patients were not required to have been experiencing fluctuations. Prior to the controlled part of these trials, patients were stabilized on levodopa for 2 - 4 weeks.

There is limited experience of using entacapone in patients who do not experience fluctuations.

In the first two studies to be described, patients were randomized to receive placebo or entacapone 200mg administered concomitantly with each dose of carbidopa-levodopa (up to 10 times daily, but averaging 4-6 doses per day). The formal double-blind portion of both trials was 6 months long. Patients recorded the time spent in the "On" and "Off" states in home diaries periodically throughout the duration of the trial. In one study, conducted in the Nordic countries, the primary outcome measure was the total mean time spent in the "On" state during an 18-hour diary recorded day (6 a.m. to midnight). In the other study, the primary outcome measure was the proportion of awake time spent over 24 hours in the "On" state.

In addition to the primary outcome measure, the amount of time spent in the "Off" state was evaluated, and patients were also evaluated by subparts of the Unified Parkinson's Disease Rating Scale (UPDRS), a frequently used multi-item rating scale intended to assess mentation (Part I), activities of daily living (Part II), motor function (Part III), complications of therapy (Part IV), and disease staging (Part V & VI); an investigator's and patient's global assessment of clinical condition, a 7-point subjective scale designed to assess global functioning in Parkinson's Disease; and the change in daily carbidopa-levodopa dose.

In one of the studies, 171 patients were randomized in 16 centers in Finland, Norway, Sweden, and Denmark (Nordic study), all of whom received concomitant levodopa plus dopa-decarboxylase inhibitor (either carbidopa-levodopa or benserazide-levodopa). In the second trial, 205 patients were randomized in 17 centers in North America (US and Canada); all patients received concomitant carbidopa-levodopa.

The following tables display the results of these two trials:

Table 2. Nordic Study

	Baseline	Change from Baseline at Month 6*	p-value vs. placebo
Primary Measure from Home Diary (from an 18-hour Diary Day)			
Hours of Awake Time "On"			
Placebo	9.2	+0.1	–
Entacapone	9.3	+1.5	<0.001
Duration of "On" time after first AM dose (hrs)			
Placebo	2.2	0.0	–
Entacapone	2.1	+0.2	<0.05
Secondary Measures from Home Diary (from an 18-hour Diary Day)			
Hours of Awake Time "Off"			
Placebo	5.3	0.0	–
Entacapone	5.5	- 1.3	<0.001
Proportion of Awake Time "On" * (%)**			
Placebo	63.8	+0.6	–
Entacapone	62.7	+9.3	<0.001
Levodopa Total Daily Dose (mg)			
Placebo	705	+14	–
Entacapone	701	- 87	<0.001
Frequency of Levodopa Daily Intakes			
Placebo	6.1	+0.1	–
Entacapone	6.2	- 0.4	<0.001
Other Secondary Measures			
	Baseline	Change from Baseline at Month 6	p-value vs. placebo
Investigator's Global (overall) % Improved**			
Placebo	–	28	–
Entacapone	–	56	<0.01
Patient's Global (overall) % Improved**			
Placebo	–	22	–
Entacapone	–	39	N.S.‡
UPDRS Total			
Placebo	37.4	-1.1	–
Entacapone	38.5	-4.8	<0.01
UPDRS Motor			
Placebo	24.6	-0.7	–
Entacapone	25.5	-3.3	<0.05
UPDRS ADL			
Placebo	11.0	-0.4	–
Entacapone	11.2	-1.8	<0.05

* Mean; the month 6 values represent the average of weeks 8, 16, and 24, by protocol-defined outcome measure

** At least one category change at endpoint.

*** Not an endpoint for this study but primary endpoint in the North American Study.

‡ Not significant.

Table 3. North American Study

	Baseline	Change from Baseline at Month 6	p-value vs. placebo
Primary Measure from Home Diary (for a 24-hour Diary Day)			
Percent of Awake Time "On"			
Placebo	60.8	+2.0	–
Entacapone	60.0	+6.7	<0.05
Secondary Measures from Home Diary (for a 24-hour Diary Day)			
Hours of Awake Time "Off"			
Placebo	6.6	- 0.3	–
Entacapone	6.8	- 1.2	<0.01
Hours of Awake Time "On"			
Placebo	10.3	+ 0.4	–
Entacapone	10.2	+ 1.0	N.S.‡
Levodopa Total Daily Dose (mg)			
Placebo	758	+ 19	–
Entacapone	804	- 93	<0.001
Frequency of Levodopa Daily Intakes			
Placebo	6.0	+ 0.2	–
Entacapone	6.2	0.0	N.S.‡
Other Secondary Measures			
	Baseline	Change from Baseline at Month 6	p-value vs. placebo
Investigator's Global (overall) % Improved**			
Placebo	–	21	–
Entacapone	–	34	<0.05
Patient's Global (overall) % Improved**			
Placebo	–	20	–
Entacapone	–	31	<0.05
UPDRS Total***			
Placebo	35.6	+2.8	–
Entacapone	35.1	-0.6	<0.05
UPDRS Motor***			
Placebo	22.6	+1.2	–
Entacapone	22.0	-0.9	<0.05
UPDRS ADL***			
Placebo	11.7	+1.1	–
Entacapone	11.9	0.0	<0.05

* Mean; the month 6 values represent the average of weeks 8, 16, and 24, by protocol-defined outcome measure.

** At least one category change at endpoint.

*** Score change at endpoint similarly to the Nordic Study.

‡ Not significant.

Effects on "On" time did not differ by age, sex, weight, disease severity at baseline, levodopa dose and concurrent treatment with dopamine agonists or selegiline.

Withdrawal of entacapone: In the North American study, abrupt withdrawal of entacapone, without alteration of the dose of carbidopa-levodopa, resulted in a significant worsening of fluctuations, compared to placebo. In some cases, symptoms were slightly worse than at baseline, but returned to approximately baseline severity within two weeks following levodopa dose increase on average by 80mg. In the Nordic study, similarly, a significant worsening of parkinsonian symptoms was observed after entacapone withdrawal, as assessed two weeks after drug withdrawal. At this phase, the symptoms were approximately at baseline severity following levodopa dose increase by about 50mg.

In the third placebo-controlled trial, a total of 301 patients were randomized in 32 centers in Germany and Austria. In this trial, as in the other two trials, entacapone 200mg was administered with each dose of levodopa/dopa decarboxylase inhibitor (up to 10 times daily) and UPDRS Parts II and III and total daily "On" time were the primary measures of effectiveness. The following results were seen for the primary measures, as well as for some secondary measures:

Table 4. German-Austrian Study

Primary Measures			
	Baseline	Change from Baseline at Month 6	p-value vs. placebo (LOCF)
UPDRS ADL*			
Placebo	12.0	+0.5	–
Entacapone	12.4	-0.4	<0.05
UPDRS Motor*			
Placebo	24.1	+0.1	–
Entacapone	24.9	-2.5	<0.05
Hours of Awake Time "On" (Home diary)**			
Placebo	10.1	+0.5	–
Entacapone	10.2	+1.1	N.S.‡

Secondary Measures			
	Baseline	Change from Baseline at Month 6	p-value vs. placebo
UPDRS Total*			
Placebo	37.7	+0.6	–
Entacapone	39.0	-3.4	<0.05
Percent of Awake Time "On" (Home diary)**			
Placebo	59.8	+3.5	–
Entacapone	62.0	+6.5	N.S.‡
Hours of Awake Time "Off" (Home diary)**			
Placebo	6.8	-0.6	–
Entacapone	6.3	-1.2	0.07
Levodopa Total Daily Dose (mg)*			
Placebo	572	+4	–
Entacapone	566	-35	N.S.‡
Frequency of Levodopa Daily Intake*			
Placebo	5.6	+0.2	–
Entacapone	5.4	0.0	<0.01
Global (overall) % Improved***			
Placebo	–	34	–
Entacapone	–	38	N.S.‡

* Total population; score change at endpoint.

** Fluctuating population, with 5-10 doses; score change at endpoint.

*** Total population; at least one category change at endpoint.

‡ Not significant.

INDICATIONS

STALEVO™ (carbidopa, levodopa and entacapone) is indicated to treat patients with idiopathic Parkinson's disease:

1) To substitute (with equivalent strength of each of the three components) for immediate release cardidopa/levodopa and entacapone previously administered as individual products.

2) To replace immediate release carbidopa/levodopa therapy (without entacapone) when patients experience the signs and symptoms of end-of-dose "wearing-off" (only for patients taking a total daily dose of levodopa of 600mg or less and not experiencing dyskinesias, see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

STALEVO™ (carbidopa, levodopa and entacapone) tablets are contraindicated in patients who have demonstrated hypersensitivity to any component (carbidopa, levodopa, or entacapone) of the drug or its excipients.

Monoamine oxidase (MAO) and COMT are the two major enzyme systems involved in the metabolism of catecholamines. It is theoretically possible, therefore, that the combination of entacapone and a non-selective MAO inhibitor (e.g., phenelzine and tranylcypromine) would result in inhibition of the majority of the pathways responsible for normal catecholamine metabolism. As with carbidopa-levodopa, nonselective monoamine oxidase (MAO) inhibitors are contraindicated for use with STALEVO. These inhibitors must be discontinued at least two weeks prior to initiating therapy with STALEVO. STALEVO may be administered concomitantly with the manufacturer's recommended dose of MAO inhibitors with selectivity for MAO type B (e.g., selegiline HCl) (See PRECAUTIONS, Drug Interactions).

STALEVO is contraindicated in patients with narrow-angle glaucoma.

Because levodopa may activate malignant melanoma, STALEVO should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS

The addition of carbidopa to levodopa reduces the peripheral effects (nausea, vomiting) due to decarboxylation of levodopa; however, carbidopa does not decrease the adverse reactions due to the central effects of levodopa. Because carbidopa as well as entacapone permits more levodopa to reach the brain and more dopamine to be formed, certain adverse CNS effects, e.g., dyskinesia (involuntary movements) may occur at lower dosages and sooner with levodopa preparations containing carbidopa and entacapone than with levodopa alone.

The occurrence of dyskinesias may require dosage reduction (see PRECAUTIONS, Dyskinesia).

STALEVO™ (carbidopa, levodopa and entacapone) may cause mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses should be treated with caution.

STALEVO should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

As with levodopa, care should be exercised in administering STALEVO to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored carefully during the period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, treatment with STALEVO may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

Neuroleptic Malignant Syndrome (NMS): Sporadic cases of a symptom complex resembling NMS have been reported in association with dose reductions or withdrawal of therapy with carbidopa-levodopa. Therefore, patients should be observed carefully when the dosage of STALEVO is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics. NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia. Neurological findings, including muscle rigidity, involuntary movements, altered consciousness, mental status changes; other disturbances, such as autonomic dysfunction, tachycardia, tachypnea, sweating, hyper- or hypotension; laboratory findings, such as creatine phosphokinase elevation, leukocytosis, myoglobinuria, and increased serum myoglobin have been reported.

The early diagnosis of this condition is important for the appropriate management of these patients. Considering NMS as a possible diagnosis and ruling out other acute illnesses (e.g., pneumonia, systemic infection, etc.) is essential. This may be especially complex if the clinical presentation includes both serious medical illness and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) intensive symptomatic treatment and medical monitoring and 2) treatment of any concomitant serious medical problems for which specific treatments are available. Dopamine agonists, such as bromocriptine, and muscle relaxants, such as dantrolene, are often used in the treatment of NMS, however, their effectiveness has not been demonstrated in controlled studies.

Drugs Metabolized By Catechol-*O*-Methyltransferase (COMT)

When a single 400mg dose of entacapone was given together with intravenous isoprenaline (isoproterenol) and epinephrine without coadministered levodopa/dopa decarboxylase inhibitor, the overall mean maximal changes in heart rate during infusion were about 50% and 80% higher than with placebo, for isoprenaline and epinephrine, respectively.

Therefore, drugs known to be metabolized by COMT, such as isoproterenol, epinephrine, norepinephrine, dopamine, dobutamine, alpha-methyldopa, apomorphine, isoetherine, and bitolterol should be administered with caution in patients receiving entacapone regardless of the route of administration (including inhalation), as their interaction may result in increased heart rates, possibly arrhythmias, and excessive changes in blood pressure.

Ventricular tachycardia was noted in one 32-year-old healthy male volunteer in an interaction study after epinephrine infusion and oral entacapone administration. Treatment with propranolol was required. A causal relationship to entacapone administration appears probable but cannot be attributed with certainty.

PRECAUTIONS

General

As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with STALEVO™ (carbidopa, levodopa and entacapone) provided the intraocular pressure is well controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.

Hypotension/Syncope

In the large controlled trials of entacapone, approximately 1.2% and 0.8% of 200mg entacapone and placebo patients treated also with levodopa/dopa decarboxylase inhibitor, respectively, reported at least one episode of syncope. Reports of syncope were generally more frequent in patients in both treatment groups who had an episode of documented hypotension (although the episodes of syncope, obtained by history, were themselves not documented with vital sign measurement).

Diarrhea

In clinical trials of entacapone, diarrhea developed in 60 of 603 (10.0%) and 16 of 400 (4.0%) of patients treated with 200mg of entacapone or placebo in combination with levodopa/dopa decarboxylase inhibitor, respectively. In patients treated with entacapone, diarrhea was generally mild to moderate in severity (8.6%) but was regarded as severe in 1.3%. Diarrhea resulted in withdrawal in 10 of 603 (1.7%) patients, 7 (1.2%) with mild and moderate diarrhea and 3 (0.5%) with severe diarrhea. Diarrhea generally resolved after discontinuation of

entacapone. Two patients with diarrhea were hospitalized. Typically, diarrhea presents within 4 - 12 weeks after entacapone is started, but it may appear as early as the first week and as late as many months after the initiation of treatment.

Hallucinations

Dopaminergic therapy in Parkinson's disease patients has been associated with hallucinations. In clinical trials of entacapone, hallucinations developed in approximately 4.0% of patients treated with 200mg entacapone or placebo in combination with levodopa/dopa decarboxylase inhibitor. Hallucinations led to drug discontinuation and premature withdrawal from clinical trials in 0.8% and 0% of patients treated with 200mg entacapone and placebo, respectively. Hallucinations led to hospitalization in 1.0% and 0.3% of patients in the 200mg entacapone and placebo groups, respectively.

Dyskinesia

Entacapone may potentiate the dopaminergic side effects of levodopa and may therefore cause and/or exacerbate preexisting dyskinesia. Although decreasing the dose of levodopa may ameliorate this side effect, many patients in controlled trials continued to experience frequent dyskinesias despite a reduction in their dose of levodopa. The rates of withdrawal for dyskinesia were 1.5% and 0.8% for 200mg entacapone and placebo, respectively.

Other Events Reported With Dopaminergic Therapy

The events listed below are rare events known to be associated with the use of drugs that increase dopaminergic activity, although they are most often associated with the use of direct dopamine agonists.

Rhabdomyolysis: Cases of severe rhabdomyolysis have been reported with entacapone when used in combination with levodopa. The complicated nature of these cases makes it impossible to determine what role, if any, entacapone played in their pathogenesis. Severe prolonged motor activity including dyskinesia may account for rhabdomyolysis. One case, however, included fever and alteration of consciousness. It is therefore possible that the rhabdomyolysis may be a result of the syndrome described in Hyperpyrexia and Confusion (see PRECAUTIONS, Other Events Reported With Dopaminergic Therapy).

Hyperpyrexia and Confusion: Cases of a symptom complex resembling the neuroleptic malignant syndrome characterized by elevated temperature, muscular rigidity, altered consciousness, and elevated CPK have been reported in association with the rapid dose reduction or withdrawal of other dopaminergic drugs. No cases have been reported following the abrupt withdrawal or dose reduction of entacapone treatment during clinical studies.

Prescribers should exercise caution when discontinuing carbidopa,levodopa andentacapone combination treatment. When considered necessary, withdrawal should proceed slowly. If a decision is made to discontinue treatment with STALEVO, recommendations include monitoring the patient closely and adjusting other dopaminergic treatments as needed. This

syndrome should be considered in the differential diagnosis for any patient who develops a high fever or severe rigidity. Tapering entacapone has not been systematically evaluated.

Fibrotic Complications: Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening have been reported in some patients treated with ergot derived dopaminergic agents. These complications may resolve when the drug is discontinued, but complete resolution does not always occur. Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived drugs (e.g., entacapone, levodopa) that increase dopaminergic activity can cause them is unknown. It should be noted that the expected incidence of fibrotic complications is so low that even if entacapone caused these complications at rates similar to those attributable to other dopaminergic therapies, it is unlikely that it would have been detected in a cohort of the size exposed to entacapone. Four cases of pulmonary fibrosis were reported during clinical development of entacapone; three of these patients were also treated with pergolide and one with bromocriptine. The duration of treatment with entacapone ranged from 7 - 17 months.

Renal Toxicity

In a one-year toxicity study, entacapone (plasma exposure 20 times that in humans receiving the maximum recommended daily dose of 1600mg) caused an increased incidence of nephrotoxicity in male rats that was characterized by regenerative tubules, thickening of basement membranes, infiltration of mononuclear cells and tubular protein casts. These effects were not associated with changes in clinical chemistry parameters, and there is no established method for monitoring for the possible occurrence of these lesions in humans. Although this toxicity could represent a species-specific effect, there is not yet evidence that this is so.

Hepatic Impairment

Patients with hepatic impairment should be treated with caution. The AUC and C_{max} of entacapone approximately doubled in patients with documented liver disease compared to controls. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, and DOSAGE AND ADMINISTRATION).

Biliary Obstruction

Caution should be exercised when administering STALEVO to patients with biliary obstruction, as entacapone is excreted mostly via the bile.

Information for Patients

The patient should be instructed to take STALEVO™ (carbidopa, levodopa and entacapone) only as prescribed. The patient should be informed that STALEVO is a standard-release formulation of carbidopa-levodopa combined with entacapone that is designed to begin release of ingredients within 30 minutes after ingestion. It is important that STALEVO be

taken at regular intervals according to the schedule outlined by the physician. The patient should be cautioned not to change the prescribed dosage regimen and not to add any additional antiparkinsonian medications, including other carbidopa-levodopa preparations, without first consulting the physician.

Patients should be advised that sometimes a "wearing-off" effect may occur at the end of the dosing interval. The physician should be notified for possible treatment-adjustments if such response poses a problem to patient's every-day life.

Patients should be advised that occasionally, dark color (red, brown, or black) may appear in saliva, urine, or sweat after ingestion of STALEVO. Although the color appears to be clinically insignificant, garments may become discolored.

The patient should be advised that a change in diet to foods that are high in protein may delay the absorption of levodopa and may reduce the amount taken up in the circulation. Excessive acidity also delays stomach emptying, thus delaying the absorption of levodopa. Iron salts (such as in multi-vitamin tablets) may also reduce the amount of levodopa available to the body. The above factors may reduce the clinical effectiveness of the levodopa, carbidopa-levodopa and STALEVO therapy.

NOTE: The suggested advice to patients being treated with STALEVO is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should be informed that hallucinations can occur.

Patients should be advised that they may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope, and sweating. Hypotension may occur more frequently during initial therapy or when total daily levodopa dosage is increased. Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods, and especially at the initiation of treatment with STALEVO.

Patients should be advised that they should neither drive a car nor operate other complex machinery until they have gained sufficient experience on STALEVO to gauge whether or not it affects their mental and/or motor performance adversely. Because of the possible additive sedative effects, caution should be used when patients are taking other CNS depressants in combination with STALEVO.

Patients should be informed that nausea may occur, especially at the initiation of treatment with STALEVO.

Patients should be advised of the possibility of an increase in dyskinesia.

Carbidopa-levodopa combination and entacapone are known to affect embryo-fetal development in the rabbit and in the rat, respectively. Accordingly, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see PRECAUTIONS, Pregnancy).

Carbidopa and entacapone are known to be excreted into maternal milk in rats. Because of the possibility that carbidopa, levodopa and entacapone may be excreted into human maternal milk, patients should be advised to notify their physicians if they intend to breastfeed or are breastfeeding an infant.

Laboratory Tests

Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in blood urea nitrogen and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of STALEVO than with levodopa.

STALEVO may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Cases of falsely diagnosed pheochromocytoma in patients on carbidopa-levodopa therapy have been reported very rarely. Caution should be exercised when interpreting the plasma and urine levels of catecholamines and their metabolites in patients on carbidopa-levodopa therapy.

Entacapone is a chelator of iron. The impact of entacapone on the body's iron stores is unknown; however, a tendency towards decreasing serum iron concentrations was noted in clinical trials. In a controlled clinical study serum ferritin levels (as marker of iron deficiency and subclinical anemia) were not changed with entacapone compared to placebo after one year of treatment and there was no difference in rates of anemia or decreased hemoglobin levels.

Drug Interactions

Caution should be exercised when the following drugs are administered concomitantly with STALEVO™ (carbidopa, levodopa and entacapone).

Anti-hypertensive agents: Symptomatic postural hypotension has occurred when carbidopa-levodopa was added to the treatment of patients receiving antihypertensive drugs. Therefore, when therapy with STALEVO is started, dosage adjustment of the antihypertensive drug may be required.

MAO inhibitors: For patients receiving nonselective MAO inhibitors, see CONTRAINDICATIONS. Concomitant therapy with selegiline and carbidopa-levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa-levodopa alone.

Tricyclic antidepressants: There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa-levodopa.

Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone) and isoniazid: Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone) and isoniazid may reduce the therapeutic effects of levodopa.

Phenytoin and papaverine: The beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with carbidopa-levodopa should be carefully observed for loss of therapeutic response.

Iron salts: Iron salts may reduce the bioavailability of levodopa, carbidopa and entacapone. The clinical relevance is unclear.

Metoclopramide: Although metoclopramide may increase the bioavailability of levodopa by increasing gastric emptying, metoclopramide may also adversely affect disease control by its dopamine receptor antagonistic properties.

Drugs known to interfere with biliary excretion, glucuronidation, and intestinal beta-glucuronidase (probenecid, cholestyramine, erythromycin, rifampicin, ampicillin and chloramphenicol): As most entacapone excretion is via the bile, caution should be exercised when drugs known to interfere with biliary excretion, glucuronidation, and intestinal beta-glucuronidase are given concurrently with entacapone. These include probenecid, cholestyramine, and some antibiotics (e.g., erythromycin, rifampicin, ampicillin and chloramphenicol).

Pyridoxine: STALEVO can be given to patients receiving supplemental pyridoxine. Oral coadministration of 10-25mg of pyridoxine hydrochloride (vitamin B6) with levodopa may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyridoxine; therefore, STALEVO can be given to patients receiving supplemental pyridoxine.

Effect of levodopa & carbidopa in STALEVO on the metabolism of other drugs: Inhibition or induction effect of levodopa & carbidopa has not been investigated.

Effect of entacapone in STALEVO on the metabolism of other drugs: Entacapone is unlikely to inhibit the metabolism of other drugs that are metabolized by major P450s including CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A. In vitro studies of human CYP enzymes showed that entacapone inhibited the CYP enzymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A only at very high concentrations (IC50 from 200 to over 1000 μM; an oral 200mg dose achieves a highest level of approximately 5 μM in people); these enzymes would therefore not be expected to be inhibited in clinical use. However, no information is available regarding the induction effect from entacapone.

Drugs that are highly protein bound (such as warfarin, salicylic acid, phenylbutazone, and diazepam)

Levodopa
Levodopa is bound to plasma protein only to a minor extent (about 10-30%).

Carbidopa
Carbidopa is approximately 36 % bound to plasma protein.

Entacapone

Entacapone is highly protein bound (98%). In vitro studies have shown no binding displacement between entacapone and other highly bound drugs, such as warfarin, salicylic acid, phenylbutazone, and diazepam.

Hormone levels

Of the ingredients in STALEVO, levodopa is known to depress prolactin secretion and increase growth hormone levels.

Carcinogenesis

In a two-year bioassay of carbidopa-levodopa, no evidence of carcinogenicity was found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa.

Two-year carcinogenicity studies of entacapone were conducted in mice and rats. Rats were treated once daily by oral gavage with entacapone doses of 20, 90, or 400mg/kg. An increased incidence of renal tubular adenomas and carcinomas was found in male rats treated with the highest dose of entacapone. Plasma exposures (AUC) associated with this dose were approximately 20 times higher than estimated plasma exposures of humans receiving the maximum recommended daily dose of entacapone (MRDD = 1600mg). Mice were treated once daily by oral gavage with doses of 20, 100 or 600mg/kg of entacapone (0.05, 0.3, and 2 times the MRDD for humans on a mg/m^2 basis). Because of a high incidence of premature mortality in mice receiving the highest dose of entacapone, the mouse study is not an adequate assessment of carcinogenicity. Although no treatment related tumors were observed in animals receiving the lower doses, the carcinogenic potential of entacapone has not been fully evaluated. The carcinogenic potential of entacapone administered in combination with carbidopa-levodopa has not been evaluated.

Mutagenesis

Carbidopa was positive in the Ames test in the presence and absence of metabolic activation, was mutagenic in the *in vitro* mouse lymphoma/thymidine kinase assay in the absence of metabolic activation, and was negative in the *in vivo* mouse micronucleus test.

Entacapone was mutagenic and clastogenic in the *in vitro* mouse lymphoma/thymidine kinase assay in the presence and absence of metabolic activation, and was clastogenic in cultured human lymphocytes in the presence of metabolic activation. Entacapone, either alone or in combination with carbidopa-levodopa, was not clastogenic in the *in vivo* mouse micronucleus test or mutagenic in the bacterial reverse mutation assay (Ames test).

Impairment of Fertility

In reproduction studies with carbidopa-levodopa, no effects on fertility were found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa.

Entacapone did not impair fertility or general reproductive performance in rats treated with up to 700mg/kg/day (plasma AUCs 28 times those in humans receiving the MRDD). Delayed mating, but no fertility impairment, was evident in female rats treated with 700mg/kg/day of entacapone.

Pregnancy

Pregnancy Category C. Carbidopa-levodopa caused both visceral and skeletal malformations in rabbits at all doses and ratios of carbidopa-levodopa tested, which ranged from 10 times/5 times the maximum recommended human dose of carbidopa-levodopa to 20 times/10 times the maximum recommended human dose of carbidopa-levodopa. There was a decrease in the number of live pups delivered by rats receiving approximately two times the maximun recommended human dose of carbidopa and approximately five times the maximum recommended human dose of levodopa during organogenesis. No teratogenic effects were observed in mice receiving up to 20 times the maximum recommended human dose of carbidopa-levodopa.

It has been reported from individual cases that levodopa crosses the human placental barrier, enters the fetus, and is metabolized. Carbidopa concentrations in fetal tissue appeared to be minimal.

In embryofetal development studies, entacapone was administered to pregnant animals throughout organogenesis at doses of up to 1000mg/kg/day in rats and 300mg/kg/day in rabbits. Increased incidences of fetal variations were evident in litters from rats treated with the highest dose, in the absence of overt signs of maternal toxicity. The maternal plasma drug exposure (AUC) associated with this dose was approximately 34 times the estimated plasma exposure in humans receiving the maximum recommended daily dose (MRDD) of

1600mg. Increased frequencies of abortions and late/total resorptions and decreased fetal weights were observed in the litters of rabbits treated with maternotoxic doses of 100mg/kg/day (plasma AUCs 0.4 times those in humans receiving the MRDD) or greater. There was no evidence of teratogenicity in these studies.

However, when entacapone was administered to female rats prior to mating and during early gestation, an increased incidence of fetal eye anomalies (macrophthalmia, microphthalmia, anophthalmia) was observed in the litters of dams treated with doses of 160mg/kg/day (plasma AUCs 7 times those in humans receiving the MRDD) or greater, in the absence of maternotoxicity. Administration of up to 700mg/kg/day (plasma AUCs 28 times those in humans receiving the MRDD) to female rats during the latter part of gestation and throughout lactation, produced no evidence of developmental impairment in the offspring.

There is no experience from clinical studies regarding the use of STALEVO in pregnant women. Therefore, STALEVO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women

In animal studies, carbidopa and entacapone were excreted into maternal rat milk. It is not known whether entacapone or carbidopa-levodopa are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when STALEVO is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Carbidopa-levodopa

The most common adverse reactions reported with carbidopa-levodopa have included dyskinesias, such as choreiform, dystonic, and other involuntary movements and nausea.

The following other adverse reactions have been reported with carbidopa-levodopa:

Body as a Whole: Chest pain, asthenia.

Cardiovascular: Cardiac irregularities, hypotension, orthostatic effects including orthostatic hypotension, hypertension, syncope, phlebitis, palpitation.

Gastrointestinal: Dark saliva, gastrointestinal bleeding, development of duodenal ulcer, anorexia, vomiting, diarrhea, constipation, dyspepsia, dry mouth, taste alterations.

Hematologic: Agranulocytosis, hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia.

Hypersensitivity: Angioedema, urticaria, pruritus, Henoch-Schönlein purpura, bullous lesions (including pemphigus-like reactions).

Musculoskeletal: Back pain, shoulder pain, muscle cramps.

Nervous System/Psychiatric: Psychotic episodes including delusions, hallucinations, and paranoid ideation, neuroleptic malignant syndrome (see WARNINGS), bradykinetic episodes ("on-off" phenomenon), confusion, agitation, dizziness, somnolence, dream abnormalities including nightmares, insomnia, paresthesia, headache, depression with or without development of suicidal tendencies, dementia, increased libido. Convulsions also have occurred; however, a causal relationship with carbidopa-levodopa has not been established.

Respiratory: Dyspnea, upper respiratory infection.

Skin: Rash, increased sweating, alopecia, dark sweat.

Urogenital: Urinary tract infection, urinary frequency, dark urine.

Laboratory Tests: Decreased hemoglobin and hematocrit; abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen (BUN), Coombs' test; elevated serum glucose; white blood cells, bacteria, and blood in the urine.

Other adverse reactions that have been reported with levodopa alone and with various carbidopa-levodopa formulations, and may occur with STALEVO™ (carbidopa, levodopa and entacapone) are:

Body as a Whole: Abdominal pain and distress, fatigue.

Cardiovascular: Myocardial infarction.

Gastrointestinal: Gastrointestinal pain, dysphagia, sialorrhea, flatulence, bruxism, burning sensation of the tongue, heartburn, hiccups.

Metabolic: Edema, weight gain, weight loss.

Musculoskeletal: Leg pain.

Nervous System/Psychiatric: Ataxia, extrapyramidal disorder, failing, anxiety, gait abnormalities, nervousness, decreased mental acuity, memory impairment, disorientation, euphoria, blepharospasm (which may be taken as an early sign of excess dosage; consideration of dosage reduction may be made at this time), trismus, increased tremor, numbness, muscle twitching, activation of latent Horner's syndrome, peripheral neuropathy.

Respiratory: Pharyngeal pain, cough.

Skin: Malignant melanoma (see also CONTRAINDICATIONS), flushing.

Special Senses: Oculogyric crisis, diplopia, blurred vision, dilated pupils.

Urogenital: Urinary retention, urinary incontinence, priapism.

Miscellaneous: Bizarre breathing patterns, faintness, hoarseness, malaise, hot flashes, sense of stimulation.

Laboratory Tests: Decreased white blood cell count and serum potassium; increased serum creatinine and uric acid; protein and glucose in urine.

Entacapone

The most commonly observed adverse events (>5%) in the double-blind, placebo-controlled trials of entacapone (N=1003) associated with the use of entacapone alone and not seen at an equivalent frequency among the placebo-treated patients were: dyskinesia/hyperkinesia, nausea, urine discoloration, diarrhea, and abdominal pain.

Approximately 14% of the 603 patients given entacapone in the double blind, placebo-controlled trials discontinued treatment due to adverse events compared to 9% of the 400 patients who received placebo. The most frequent causes of discontinuation in decreasing order are: psychiatric reasons (2% vs. 1%), diarrhea (2% vs. 0%), dyskinesia/hyperkinesia (2% vs. 1%), nausea (2% vs. 1%), abdominal pain (1% vs. 0%), and aggravation of Parkinson's disease symptoms (1% vs. 1%).

Adverse Event Incidence in Controlled Clinical Studies of Entacapone

Table 6 lists treatment emergent adverse events that occurred in at least 1% of patients treated with entacapone participating in the double blind, placebo-controlled studies and that were numerically more common in the entacapone group, compared to placebo. In these studies, either entacapone or placebo was added to carbidopa-levodopa (or benserazide-levodopa).

Table 5. Summary of Patients with Adverse Events after Start of Trial Drug Administration. At least 1% in Entacapone Group and > Placebo

SYSTEM ORGAN CLASS Preferred term	Entacapone (n = 603) % of patients	Placebo (n = 400)) % of patients
SKIN AND APPENDAGES DISORDERS		
Sweating increased	2	1
MUSCULOSKELETAL SYSTEM DISORDERS		
Back pain	2	1
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS		
Dyskinesia	25	15
Hyperkinesia	10	5
Hypokinesia	9	8
Dizziness	8	6
SPECIAL SENSES, OTHER DISORDERS		
Taste Perversion	1	0
PSYCHIATRIC DISORDERS		
Anxiety	2	1
Somnolence	2	0
Agitation	1	0
GASTROINTESTINAL SYSTEM DISORDERS		
Nausea	14	8
Diarrhea	10	4
Abdominal Pain	8	4
Constipation	6	4
Vomiting	4	1
Mouth dry	3	0
Dyspepsia	2	1
Flatulence	2	0
Gastritis	1	0
Gastrointestinal Disorders nos	1	0
RESPIRATORY SYSTEM DISORDERS		
Dyspnea	3	1
PLATELET, BLEEDING & CLOTTING DISORDERS		
Purpura	2	1
URINARY SYSTEM DISORDERS		
Urine Discoloration	10	0
BODY AS A WHOLE - GENERAL DISORDERS		
Back Pain	4	2
Fatigue	6	4
Asthenia	2	1
RESISTANCE MECHANISM DISORDERS		
Infection Bacterial	1	0

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures do, however, provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse events observed in the population studied.

Effects of gender and age on adverse reactions

No differences were noted in the rate of adverse events attributable to entacapone alone by age or gender.

DRUG ABUSE AND DEPENDENCE

Controlled substance class- STALEVO™ (carbidopa, levodopa and entacapone) is not a controlled substance.

Physical and psychological dependence- STALEVO has not been systematically studied, in animal or humans, for its potential for abuse, tolerance or physical dependence. In premarketing clinical experience, carbidopa-levodopa did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. However, there are rare postmarketing reports of abuse and dependence of medications containing levodopa. In general, these reports consist of patients taking increasing doses of medication in order to achieve an euphoric state.

OVERDOSAGE

Management of acute overdosage with STALEVO™ (carbidopa, levodopa and entacapone) is the same as management of acute overdosage with levodopa and entacapone. Pyridoxine is not effective in reversing the actions of STALEVO.

Hospitalization is advised, and general supportive measures should be employed, along with immediate gastric lavage and repeated doses of charcoal over time. This may hasten the elimination of entacapone in particular, by decreasing its absorption/reabsorption from the GI tract. Intravenous fluids should be administered judiciously and an adequate airway maintained.

The adequacy of the respiratory, circulatory and renal systems should be carefully monitored and appropriate supportive measures employed. Electrocardiographic monitoring should be instituted and the patient carefully observed for the development of arrhythmias; if required, appropriate anti-arrhythmic therapy should be given. The possibility that the patient may have taken other drugs, increasing the risk of drug interactions (especially catechol-structured drugs) should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known. Hemodialysis or hemoperfusion is unlikely to reduce entacapone levels due to its high binding to plasma proteins.

There are very few cases of overdosage with levodopa reported in the published literature. Based on the limited available information, the acute symptoms of levodopa/dopa decarboxylase inhibitor overdosage can be expected to arise from dopaminergic overstimulation. Doses of a few grams may result in CNS disturbances, with an increasing likelihood of cardiovascular disturbance (e.g. hypotension, tachycardia) and more severe psychiatric problems at higher doses. An isolated report of rhabdomyolysis and another of transient renal insufficiency suggest that levodopa overdosage may give rise to systemic complications, secondary to dopaminergic overstimulation.

There have been no reported cases of either accidental or intentional overdose with entacapone tablets. However, COMT inhibition by entacapone treatment is dose-dependent. A massive overdose of entacapone may theoretically produce a 100% inhibition of the COMT enzyme in people, thereby preventing the O-methylation of endogenous and exogenous catechols.

The highest single dose of entacapone administered to humans was 800mg, resulting in a plasma concentration of 14.1 µg/mL. The highest daily dose given to humans was 2400mg, administered in one study as 400mg six times daily with carbidopa-levodopa for 14 days in 15 Parkinson's disease patients, and in another study as 800mg t.i.d. for 7 days in 8 healthy volunteers. At this daily dose, the peak plasma concentrations of entacapone averaged 2.0 µg/mL (at 45 min., compared to 1.0 and 1.2 µg/mL with 200mg entacapone at 45 min.). Abdominal pain and loose stools were the most commonly observed adverse events during this study. Daily doses as high as 2000mg entacapone have been administered as 200mg 10 times daily with carbidopa-levodopa or benserazide-levodopa for at least 1 year in 10 patients, for at least 2 years in 8 patients and for at least 3 years in 7 patients. Overall, however, clinical experience with daily doses above 1600mg is limited.

The range of lethal plasma concentrations of entacapone based on animal data was 80 - 130 µg/mL in mice. Respiratory difficulties, ataxia, hypoactivity, and convulsions were observed in mice after high oral (gavage) doses.

DOSAGE AND ADMINISTRATION

Individual tablets should not be fractionated and only one tablet should be administered at each dosing interval.

Generally speaking, STALEVO should be used as a substitute for patients already stabilized on equivalent doses of carbidopa-levodopa and entacapone. However, some patients who have been stabilized on a given dose of carbidopa/levodopa may be treated with STALEVO if a decision has been made to add entacapone (see below).

The optimum daily dosage of STALEVO™ (carbidopa, levodopa and entacapone) must be determined by careful titration in each patient. STALEVO tablets are available in three strengths, each in a 1:4 ratio of carbidopa to levodopa and combined with 200mg of entacapone in a standard release formulation (STALEVO 50 containing 12.5mg of carbidopa,

50mg of levodopa and 200mg of entacapone; STALEVO 100 containing 25mg of carbidopa, 100mg of levodopa and 200mg of entacapone; and STALEVO 150 containing 37.5mg of carbidopa, 150mg of levodopa and 200mg of entacapone).

Therapy should be individualized and adjusted according to the desired therapeutic response.

Studies show that peripheral dopa decarboxylase is saturated by carbidopa at approximately 70 to 100mg a day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting. Experience with total daily dosages of carbidopa greater than 200mg is limited.

Clinical experience with daily doses above 1600mg of entacapone is limited. It is recommended that no more than one STALEVO tablet be taken at each dosing administration. Thus the maximum recommended daily dose of STALEVO is eight tablets per day.

How to transfer patients taking carbidopa-levodopa preparations and Comtan® (entacapone) tablets to STALEVO™ (carbidopa, levodopa and entacapone) tablets

There is no experience in transferring patients currently treated with formulations of carbidopa-levodopa other than immediate release carbidopa-levodopa with a 1:4 ratio (controlled release formulations, or standard release presentations with a 1:10 ratio of carbidopa-levodopa) and entacapone to STALEVO.

Patients who are currently treated with Comtan 200mg tablet with each dose of standard release carbidopa-levodopa, can be directly switched to the corresponding strength of STALEVO containing the same amounts of levodopa and carbidopa. For example, patients receiving one tablet of standard release carbidopa-levodopa 25/100mg and one tablet of Comtan 200mg at each administration can be switched to a single STALEVO 100 tablet (containing 25mg of carbidopa, 100mg of levodopa and 200mg of entacapone).

How to transfer patients not currently treated with Comtan® (entacapone) tablets from carbidopa-levodopa to STALEVO™ (carbidopa, levodopa and entacapone) tablets

In patients with Parkinson's disease who experience the signs and symptoms of end-of-dose "wearing-off" on their current standard release carbidopa-levodopa treatment, clinical experience shows that patients with a history of moderate or severe dyskinesias or taking more than 600mg of levodopa per day are likely to require a reduction in daily levodopa dose when entacapone is added to their treatment. Since dose adjustment of the individual components is impossible with fixed dose products, it is recommended that patients first be titrated individually with a carbidopa-levodopa product (ratio 1:4) and an entacapone product, and then transferred to a corresponding dose of STALEVO once the patient's status has stabilized.

In patients who take a total daily levodopa dose up to 600mg, and who do not have dyskinesias, an attempt can be made to transfer to the corresponding daily dose of STALEVO. Even in these patients, a reduction of carbidopa-levodopa or entacapone may be necessary however, and the provider is reminded that this may not be possible with STALEVO. Since entacapone prolongs and enhances the effects of levodopa, therapy should be individualized and adjusted if necessary according to the desired therapeutic response.

Maintenance of STALEVO treatment

Therapy should be individualized and adjusted for each patient according to the desired therapeutic response.

When less levodopa is required, the total daily dosage of carbidopa-levodopa should be reduced by either decreasing the strength of STALEVO at each administration or by decreasing the frequency of administration by extending the time between doses.

When more levodopa is required, the next higher strength of STALEVO should be taken and/or the frequency of doses should be increased, up to a maximum of 8 times daily and not to exceed the maximum daily dose recommendations as outlined above.

Addition of Other Antiparkinsonian Medications

Standard drugs for Parkinson's disease may be used concomitantly while STALEVO is being administered, although dosage adjustments may be required.

Interruption of Therapy

Sporadic cases of a symptom complex resembling Neuroleptic Malignant Syndrome (NMS) have been associated with dose reductions and withdrawal of levodopa preparations. Patients should be observed carefully if abrupt reduction or discontinuation of STALEVO is required, especially if the patient is receiving neuroleptics. (See WARNINGS.)

If general anesthesia is required, STALEVO may be continued as long as the patient is permitted to take fluids and medication by mouth. If therapy is interrupted temporarily, the patient should be observed for symptoms resembling NMS, and the usual daily dosage may be administered as soon as the patient is able to take oral medication.

Special populations

Patients With Impaired Hepatic Function:

Patients with hepatic impairment should be treated with caution. The AUC and C_{max} of entacapone approximately doubled in patients with documented liver disease, compared to controls. However, these studies were conducted with single-dose entacapone without levodopa/dopa decarboxylase inhibitor coadministration, and therefore the effects of liver disease on the kinetics of chronically administered entacapone have not been evaluated (see CLINICAL PHARMACOLOGY, Pharmacokinetics of Entacapone).

HOW SUPPLIED

STALEVO™ (carbidopa, levodopa and entacapone) is supplied as film-coated tablets for oral administration in the following three strengths:

STALEVO 50 film-coated tablets containing 12.5mg of carbidopa, 50mg of levodopa and 200mg of entacapone.
The round, bi-convex shaped tablets are brownish- or greyish-red, unscored, and embossed "LCE 50" on one side.
HDPE bottle of 100 tablets.....NDC 0078-0407-05
HDPE bottle of 250 tablets.....NDC 0078-0407-28

STALEVO 100 film-coated tablets containing 25mg of carbidopa, 100mg of levodopa and 200mg of entacapone.
The oval-shaped tablets are brownish- or greyish-red, unscored, and embossed "LCE 100" on one side.
HDPE bottle of 100 tablets.....NDC 0078-0408-05
HDPE bottle of 250 tablets.....NDC 0078-0408-28

STALEVO 150 film-coated tablets containing 37.5mg of carbidopa, 150mg of levodopa and 200mg of entacapone
The elongated-ellipse shaped tablets are brownish- or greyish-red, unscored, and embossed "LCE 150" on one side.
HDPE bottle of 100 tablets.....NDC 0078-0409-05
HDPE bottle of 250 tablets.....NDC 0078-0409-28

Store at 25°C (77°F) excursions permitted to 15°-30°C (59°-86°F).
[See USP Controlled Room Temperature.]

STALEVO™ (carbidopa, levodopa and entacapone) tablets are manufactured by Orion Corporation, Orion Pharma (Espoo, Finland) and marketed by Novartis Pharmaceuticals Corporation (East Hanover, N.J. 07936, U.S.A.).

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REV: April 2003 Printed in U.S.A. XXXXXXX